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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

MAY 1940

THE MEDICAL MANAGEMENT OF HYPERTHYROIDISM*

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TERMINOLOGY

THE term "hyperthyroidism" will be employed, for convenience, throughout this discussion to embrace all of the clinical states variously termed Graves' syndrome;[1] Basedow's disease;[2] exophthalmic goiter;[3] toxic adenoma;[4] and adenomatous goiter with hyperfunction.[5] The multiple terminology suggests the uncertain state of our knowledge. Historically, the captions lack accuracy, since the earliest satisfactory description was that of Caleb Parry[6] of Bath (1786). Clinically and physiologically, the implications of the nomenclature are even more disturbing. Exophthalmic goiter may be present without exophthalmos or goiter.[7] "Toxic adenoma"[8] implies a metabolic abnormality whose existence is doubtful. The term hyperthyroidism suggests, in the thyroid gland, an increased secretory activity which has never been demonstrated.[9]

DEFINITION

Clinical hyperthyroidism is commonly delineated by cataloguing the major symptoms of tachycardia, tremor, exophthalmos and goiter, to-

* Presented October 26, 1939, at The New York Academy of Medicine in the Twelfth Graduate Fortnight.

gether with the minor manifestations which include nervousness, sweating, asthenia and diarrhea. To these clinical manifestations, has been added the laboratory evidence of elevation of the basal metabolic rate. The relationship of these diverse phenomena may be clarified by a consideration of the physiology of the thyroid, its related glands and the involuntary nervous system.

The Physiology of the Thyroid Gland

The parenchymal cells of the thyroid gland abstract iodine[10] and tryptophan[11] from the circulating fluids and manufacture (a) a specific iodine-containing hormone, thyroxin[12] and (b) a colloid substance in which the iodine or thyroxin is stored in the thyroid lumina.

Thyroxin probably leaves the gland through both lymphatics and veins. Since the concentration of thyroxin in the blood of human patients cannot be directly measured, the demonstration of the hyperthyroid state is dependent upon presumptive evidence which is (a) histologic (b) pharmacologic (c) chemical.

(a) Histologic inferences concerning the hyperthyroid state are based on the hyperplasia[13] of the gland that is commonly, but not invariably, observed. Hyperplasia of the gland is not limited to hyperthyroidism. It may occur in simple or endemic goiter[14] or human cretinism.[15] The histological picture is independent of thyroid function but is dependent upon iodine storage,[16] a decreased concentration of the element giving rise to hyperplasia. The tenet that hyperplasia indicates hypersecretion is not in accord with fact.[17]

(b) Indirect pharmacological evidence of the presence of hyperthyroidism has been suggested through the resemblance of the clinical syndrome to the symptoms produced artificially by the ingestion of thyroid extract or the injection of crystalline thyroxin.[18] Unfortunately, the pharmacologic resemblance to clinical hyperthyroidism is imperfect. Carlson,[19] after extensive studies of thyroid feeding stated: "It would require considerable imagination or an undue influence of one's wish or one's judgment to identify the symptom-complex of excessive thyroid feeding in experimental animals with exophthalmic goiter." Every clinician has known many patients who have taken thyroid extract over long periods of time in order to effect weight reduction. These patients manifest transitory symptoms as the result of over-dosage with the drug. The symptoms abate when the drug has been discontinued and disposed of.

If true hyperthyroidism develops, it is a rare experience and more likely coincidental than of causal relationship. Exophthalmos is a prominent feature of clinical hyperthyroidism, yet it cannot be produced by thyroid feeding; it is frequently not ameliorated significantly by thyroidectomy[20] and may even progress in the face of an operative procedure sufficient to cause myxedema.[21] Poisoning with thyroid extract is not identical with clinical hyperthyroidism, though the two conditions have much in common.

(c) Indirect chemical inferences pertaining to hyperthyroidism have been suggested by studies of iodine metabolism. Low iodine figures in the blood are consistently found in endemic goiter.[22] In clinical hyperthyroidism, both high[23] and normal[24] quantities have been described—the latter particularly in patients whose disease has existed for more than a year. Failure to demonstrate a consistently increased blood iodine may not necessarily argue against the possibility of hyperthyroidism. It indicates merely that the ratio of manufacture to destruction or excretion of the hormone does not consistently lead to increased blood concentration. Curtis and Phillips[25] studied the entire iodine economy in patients with hyperthyroidism. They demonstrated a negative balance due to excessive loss of iodine in urine, blood, sweat and stool and suggested that there is a true "iodine diabetes" in hyperthyroidism. Even this important and interesting work leaves much to be desired of indirect evidence that hyperthyroidism exists. If hyperiodinemia suggests hyperthyroidism, what is the explanation of the relief of symptoms attendant upon iodine therapy? Surely, if increased blood iodine indicates hyperthyroidism, an added supply of the element should augment rather than ameliorate symptoms.

Though this hypothesis of hyperthyroidism is fascinating, the hyperthyroid state cannot be proven directly, by measurement, or indirectly by inferences from histologic, pharmacologic or chemical investigation.

The state of confusion concerning hyperthyroidism has been increased by theories concerning the toxicity of adenomata and the possible production of an altered thyroid secretion causing so-called "hyperdysthyroidism." The known facts concerning thyroid adenomata may be briefly summarized. Interpolated in the thyroid tissue, as in all other parenchymal tissue, there are frequently observed isolated and encapsulated rests or adenomata.[5] These function less actively than the nontumor tissue of the surrounding gland.[26] They cannot of themselves in-

dependently hypersecrete or give rise to clinical symptomatology except to participate in a process initiated and perpetuated by the surrounding non-tumor tissue. There is no evidence of the secretion of an altered thyroxin molecule. Hypotheses suggesting toxicity of adenomata and the existence of hyperdysthyroidism[27] not only lack positive proof but there is much tangible evidence to refute their accuracy.

Though laboratory evidence is lacking for proof of the hyperthyroid state, it is a clinical fact that subtotal thyroidectomy[28,29] relieves most of the distressing symptoms of patients suffering from clinical hyperthyroidism. There is much to suggest that the role of the thyroid may be intermediary. The amelioration of symptoms following thyroidectomy may be due not only to a decrease in the production capacity of the thyroid gland but to the severance of a link in a chain of disturbed physiological mechanisms. If the role of the thyroid gland be of secondary importance in clinical hyperthyroidism, the aim of specific therapeutic procedure would be directed toward the correction of the more fundamental disturbance. In consequence, the possible participation of factors other than the thyroid gland warrants scrutiny. These factors may be sought (a) in internal secretory glands other than the thyroid, (b) in the involuntary nervous system, (c) in a psychosomatic mechanism of basic biologic significance.

(a) There are many clinical observations that suggest, in hyperthyroidism, a primary disturbance of internal secretory glands, other than the thyroid, with secondary thyroid participation:

1) Halsted[30] was so impressed with the thymic enlargement in hyperthyroidism, that he advocated and performed thymectomy.

2) Clinically, there are many interesting inter-relationships between thyroid and ovary. Women greatly outnumber men in the incidence of hyperthyroidism. Since amenorrhea is a frequent symptom of the disturbance, the various ovarian extracts have been employed[31]—all unsuccessfully.

3) An inter-relationship of thyroid and adrenal medulla was suggested by the work of Cannon and his collaborators.[32,33] Attempts were made to prove the existence of an increased output of epinephrin or a "sensitization" of the involuntary nervous system to the action of the epinephrin through synergism with thyroxin. These experiments, though they could not be confirmed, induced Crile[34] to approach the surgical therapy of clinical hyperthyroidism by denervation of the adrenal

medulla or partial removal of its substance, a practice not generally accepted and now abandoned.

4) Marine[35] demonstrated an inter-relationship between adrenal cortex and thyroid. Destruction or freezing of cortex led to elevation of the basal metabolic rate and simulation, in laboratory animals, of clinical hyperthyroidism. Extracts of adrenal cortex are being tried therapeutically, but to no great avail, thus far.[36]

5) More recently, Collip and others[37] isolated a thyrotropic substance in the anterior pituitary gland. Occasionally, a suggestion of the clinical inter-relationship is seen in the association of pituitary syndromes and hyperthyroidism. The thyrotropic hormone may produce, in laboratory animals, a syndrome simulating clinical hyperthyroidism. It does not seem reasonable to assume, however, that this is, in truth, the sole operating mechanism. The sella turcica has been irradiated[38] in the attempt to treat hyperthyroidism by reduction or inhibition of the thyrotropic hormone. This has yielded no clinical success. Because of the presumptive inhibition of the gonadotropic factor of the pituitary gland by the male sex hormone, testosterone has been employed[39] in an attempt to inhibit the thyrotropic factor as well. The results thus far have not been encouraging.

The present status of the inter-relationship of thyroid and other internal secretory glands may be summarized briefly. Many important interplays are demonstrable. These relationships are interesting and suggestive but therapeutically unfruitful. However, these physiological approaches to the elucidation of the mechanism of hyperthyroidism indicate a mechanism beyond the thyroid gland and suggest that, one day, our present forms of therapy may be "rendered archaic by the discovery, for the control of the disturbance, of some specific physiological or pharmacological agent."[40]

(b) The failure of the clinical physiologist to unravel the riddle of hyperthyroidism, through humoral mechanisms and glandular interplay, has led to many ingenious experiments bearing on a neurogenic mechanism via the involuntary nervous system. The presenting symptoms in clinical hyperthyroidism are sympathomimetic[41]—this term indicating that they may be produced by emotional or chemical stimulation of the thoraco-lumbar portion of the involuntary nervous system. Whatever may be the ultimate agency producing hyperthyroidism there is no doubt but that eventually the causative mechanism operates through the

intervention of the involuntary nervous system. Hence, it may be profitable to review the pertinent facts relative to these neurogenic structures.

The involuntary nervous system, sometimes called the autonomic or sympathetic nervous system, operates at a level below the threshhold of consciousness, probably through centers located in the midbrain. Peripherally, it is subdivided into two mutually antagonistic divisions. The cranio-sacral or vagus system, with its characteristic pharmacodynamic responses to atropine and the acetylcholin group of drugs, need not occupy our attention. The vagal antagonist, the thoraco-lumbar or sympathetic system is certainly involved in the pathogenesis of hyperthyroidism. This system is stimulated by drugs such as adrenalin, producing sympathomimetic manifestations identical with the symptoms of hyperthyroidism.

We are ignorant of the factors that control the tonicity of the involuntary nervous system. With the exception of epinephrin, the principles derived from the ductless glands are not sympathomimetic. Were a state of hyperepinephrinemia demonstrable, the problem of hyperthyroidism might be considerably simplified but this state does not and cannot exist as shown by the assays, performed by Stewart and Rogoff,[42] of the blood of the inferior vena cava pocket. The fascinating and suggestive hypothesis of "emergency" hyperepinephrinemia[43] fails of physiological proof.

Studies of the electrolytes of the blood do not clarify the situation. The experiments of Soffer and his associates,[44] demonstrating specific diminution of organically bound magnesium in hyperthyroidism, may have important significance that is not evident today.

If physiologic and pharmacologic methods have failed to elucidate the role of the involuntary nervous system in hyperthyroidism, many clinical observations are suggestive. Virtually all patients who develop hyperthyroidism give a history of a preëxistent instability of the involuntary nervous system, a clinical state for which Kessel and Hyman[45] suggested the name "Autonomic Imbalance". Autonomic imbalance is usually the precursor or diathesis on which hyperthyroidism is superimposed, when a metabolic disturbance, characterized by increased catabolism, supervenes. When the metabolic state is restored to normalcy the patient reverts to autonomic imbalance and the residual symptoms following the relief of hyperthyroidism are identical with the early symptoms of the constitutional autonomic imbalance.

(c) Patients with autonomic imbalance present psychic and emotional instability and a bewildering variety of functional disturbances in organs whose parenchymae show no evidence of organic change. The catalogue of symptoms and signs in autonomic imbalance include vasomotor instability, manifested by cold hands and feet with or without excessive sweating; flushing; blushing; blanching; urticaria and other neurodermatitides; lability of the pulse rate and blood pressure; disturbances in motility and tonicity of smooth muscle; and secretory alterations in glandular structures. Though the manifestations of autonomic imbalance may be legion, each patient presents an individual "reaction picture" evoked by emotion, fatigue or the introduction of specific drugs. There is no significant elevation of the basal metabolic rate. The thyroid gland may be normal. There are no positive laboratory findings that are pertinent to the symptomatology. There may be present the alterations in the adrenalin sensitivity and the creatin metabolism believed respectively by Goetsch [46] and Shorr[47] to be specific for hyperthyroidism.

The concept of autonomic imbalance is essential to the understanding of the problem of hyperthyroidism. Inherent in the discussion of the mechanism of hyperthyroidism is the consideration of the factors that regulate the tonicity of the involuntary nervous system. The knowledge of either one of these problems will go far to the solution of the other. Since thyroxin is not sympathomimetic and there is no proof that sympathomimetic activity can give rise, directly or indirectly, to significant augmentation of thyroxin effect, we are compelled to admit our ignorance of the mechanism by which these agencies participate in the production of hyperthyroidism.

If the mechanism of hyperthyroidism cannot be fully explained by humoral or neurogenic factors, it may not be amiss to inquire into broader biological implications.

Biologically speaking, thyroxin is not essential to life. Phylogenetically, the gland is first observed in amphibians where its function is characterized by (1) accelerating metamorphosis, in species that normally undergo this change or (2) actually producing metamorphosis in certain salamanders which, in nature, undergo no metamorphosis. These changes have led Uhlenhuth[48] to state: "They demonstrate at what a phylogenetic stage the amphibians and perhaps the entire higher vertebrates would be if they had not developed the thyroid mechanism." In the higher vertebrates the main and, perhaps, the sole function of thy-

roxin is as a catabolist accelerating most, if not all, biologic and metabolic processes. Whether or not thyroxin contributes new functions is an academic point which need not concern us at this time. The phylogenetic appearance of the thyroid gland at the amphibian level and its catalytic function in the human economy are of profound significance in discussions of the etiology and pathogenesis of hyperthyroidism. To the best of our knowledge, hyperthyroidism occurs spontaneously only in man, and perhaps only in civilized man. McCarrison,[49] for example, never observed hyperthyroidism in the native Indian until Indian troops were sent to the First World War.

There is presumptive evidence that hyperthyroidism may be a disturbance of historically recent origin and that its incidence is rapidly increasing. The clinical appearance of the patient with hyperthyroidism is dramatic, easily recognizable and unforgetable. Though endemic goiter was known to the Egyptian and Grecian physicians and the painters of primitives, the first medical description of hyperthyroidism appeared in 1802. The four pioneers who described cases between 1802 and 1840, Flajani in Italy, Parry who practiced in Bath from 1780 to 1816, Graves of Dublin and von Basedow of Merseburg, reported a total of but fifteen patients. Certainly a practitioner today, comparable to Parry practicing in Bath for thirty-six years, sees more than five cases of hyperthyroidism. Could Parry, once recognizing hyperthyroidism, have missed other cases that occurred in his practice or was the disease so rare that he saw on the average but one case every seven years? The speculation is not idle, for if hyperthyroidism is a condition of recent origin and vastly increased incidence occurring only or almost exclusively in civilized man, the psychic component in its etiology and pathogenesis assumes greater importance. The explanation of our inability to observe or produce the syndrome in its entirety in experimental animals or to comprehend its mechanism in the clinic may rest on these biological and psychological grounds.

Etiology and Pathogenesis

From what has been said, it is apparent that we are today ignorant of the etiology and pathogenesis of hyperthyroidism. Not so long ago it was considered heresy to doubt that clinical hyperthyroidism was other than a syndrome produced by an increased output of the thyroid hormone. Today, all serious students of hyperthyroidism entertain con-

siderable doubt concerning the mechanism of this fascinating and baffling condition. Means[21] in his recent and excellent treatise on the thyroid gland and its disorders writes: "Since, in the majority of cases of exophthalmic goiter, no etiologic agent or likely causative factor thus far has been found and since the disease has not been perfectly reproduced in experimental animals, it must be admitted freely that, in contrast to endemic goiter, the cause of the disease remains quite unknown." Hoover[9] averred: "There is certainly no evidence of superfunction of the thyroid gland. All the evidence seems to indicate that hyperplasia, so called, is evidence of incompetence of the gland and is associated with hypofunction rather than hyperfunction."

Our knowledge of clinical hyperthyroidism may be summarized by the statement that it is a complicated syndrome consisting of neurogenic, metabolic and glandular components. There are present (a) a diminished storage of iodine in the thyroid gland, giving rise to hyperplasia; (b) a collection of sympathomimetic symptoms and (c) a general increase in the catabolic processes, the latter alleviated temporarily by iodine therapy and more lastingly by thyroidectomy. No one of the components of clinical hyperthyroidism is pathognomic. Increase in the catabolic processes may occur in conditions unassociated with disturbances in the thyroid gland or the involuntary nervous system. Sympathomimetic manifestations may be present with or without alterations in the thyroid gland or the basal metabolic rate. Thyroid hyperplasia may occur in otherwise normal individuals, and in patients with an elevated or diminished basal metabolic rate.

The complete clinical picture of hyperthyroidism consists in the simultaneous presence of the three abnormalities. The autonomic imbalance precedes and is the precursor of hyperthyroidism. When the catabolic phenomena are superimposed the clinical picture of hyperthyroidism is complete. When the catabolic process has abated the autonomic imbalance persists and somehow, somewhere in the pathogenesis of this process there enters the exciting factor of a psychosomatic relationship that seems to be related to the phylogenetic approach to what we call civilization.

Diagnosis

Frank hyperthyroidism seldom presents difficulty in diagnosis. Sympathomimetic manifestations and evidences of increased catabolism,

resulting in loss of weight and strength despite normal or increased alimentation, suggest examination of the thyroid gland, and estimation of the basal metabolic rate. The therapeutic test of the response to iodine furnishes complete confirmation that clinical hyperthyroidism exists.

Since determination of the basal rate requires the coöperation of patients who, because of their illness, find difficulty in offering the ideal tranquility so essential to the test, a strictly objective diagnostic measure has been sought. Goetsch[46] attempted to utilize the adrenalin response for this purpose. The presence of the adrenalin sensitivity in approximately 25 per cent of normal individuals and in a greater proportion of those with autonomic imbalance resulted in the abandonment of the Goetsch test. More recently Shorr[47] attempted to employ for diagnostic purposes the disturbance in creatin metabolism. King and Sohval[50] question the specificity of the metabolic disturbance since it was demonstrable in normal individuals, in patients with autonomic imbalance, and might be occasionally absent in patients with frank hyperthyroidism. The latter investigators concluded that "clinical judgment surpasses in value any of these laboratory aids."

It should be a comparatively simple matter to differentiate patients with clinical hyperthyroidism from those with simple thyroid enlargement whether diffuse or nodular, hyperplastic, colloidal or adenomatous. Simple thyroid enlargement is unassociated with sympathomimetic activity or an elevation of the basal metabolic rate, even when an anxiety state of "goiterophobia" is engrafted on the anatomical defect.

Patients with autonomic imbalance are all too frequently treated as sufferers from hyperthyroidism. Clinical differentiation should be simple on the basis of the long standing history in simple autonomic imbalance, the absence of clinical evidence of increased catabolism and the normal basal metabolic rate. Elevation of the basal rate determined under ideal conditions and confirmed by repeated tests, which sometimes requires institutionalization of the patient, suggests the transition from simple autonomic imbalance to true hyperthyroidism.

Patients with autonomic imbalance who dwell in a goiter belt and present the combination of sympathomimetic symptoms and a lump in the neck, with or without goiterophobia, are almost certain to be told sooner or later that they suffer from a *forme fruste* of hyperthyroidism or a true clinical hyperthyroidism, particularly if the goiter is nodular, suggesting the presence of so-called toxic adenomata. Prophylactic thy-

roidectomy may be strongly urged. This procedure, in my opinion, is needless and unjustified. Determination of the basal metabolic rate is here of inestimable value for it will be normal in the absence of clinical hyperthyroidism, despite the association of autonomic imbalance, endemic goiter and goiterophobia.

Psychotic patients in manic phases, such as occur in the agitated depressions and the manic depressive states, may present a picture suggesting hyperthyroidism. It is impossible to determine the basal metabolic rate under these circumstances. It may require a prolonged period of study and a fine sense of clinical values to differentiate the two conditions. The therapeutic response to iodine is an important differential.

The diagnostic difficulties aforementioned deal with conditions in which clinical hyperthyroidism is erroneously diagnosed. A more serious error is the failure to recognize occult hyperthyroidism, in patients presenting atypical manifestations. Occult hyperthyroidism occurs most commonly in older patients who rarely present exophthalmos and whose sympathomimetic manifestations may be mild and unrecognized. To add to the diagnostic dilemma the thyroid enlargement may be negligible. The presence of the thyroid tumor may be missed if the swelling is retrosternal, intrathoracic or hidden beneath the muscles of the neck. If the thyroid tumor is of long duration its importance may be discounted in the interpretation of the more recent symptomatology. This group of older patients, presenting little exophthalmos and a long standing thyroid tumor, correspond to Plummer's[4] group of patients with secondary hyperthyroidism or toxic adenomata. The presenting symptoms in occult hyperthyroidism may be related to the circulatory system. Boas[51] has described a group of patients who seemingly suffered from an inexplicable hypertension. White,[52] whose practice is fairly limited to patients with circulatory disorders, found that 1 per cent were thyrocardiac invalids whose circulatory damage resulted from unrecognized and long standing hyperthyroidism. Another group with occult hyperthyroidism present asthenia and loss of weight. Malignant disease is suspected and the diagnosis of clinical hyperthyroidism may be overlooked. A notable feature of surgical therapy in occult hyperthyroidism, particularly in those with thyrocardiac manifestations, is the tolerance to staged operative procedure. Patients whose circulatory status would seem to indicate desperate risk often progress with amazing and gratifying equanimity.

It is a wise precaution to exclude active tuberculosis in every instance of suspected hyperthyroidism. Sympathomimetic manifestations are commonly encountered in patients with incipient tuberculosis. The febrile process, due to the infection, causes elevation of the basal metabolic rate. Temperature records should be written at four hour intervals for at least forty-eight hours. Careful examination of the chest, including radiography, must be performed if serious errors are to be avoided.

The Clinical Types of Hyperthyroidism

No two patients with hyperthyroidism present symptom-complexes that are exactly similar. Stated positively, each patient with hyperthyroidism presents an individual symptom-complex. Plummer[4] believed that the clinical types were caused by alteration in the thyroid molecule. He differentiated between true hyperthyroidism resulting from an increased output of the normal thyroxin molecule and a second type of hyperthyroidism due to an increased output of an altered thyroid molecule. In primary hyperthyroidism the patients were younger. Exophthalmos was common. The thyroid gland was diffusely enlarged. The history of metabolic disturbance was of relatively short duration. The response to iodine was favorable and the suggested surgical procedure was the approach to subtotal thyroidectomy. Those with toxic adenomata were in the older group. Exophthalmos might be negligible or absent. The history was of long duration. The thyroid enlargement presented isolated nodules, presumably toxic adenomata. The response to iodine was variable and might even be noxious. The operative procedure was removal of the adenomatous nodule without necessarily reducing the surrounding non-tumor tissue.

The hypotheses on which this differentiation was based have never been proven. It is my belief that the variations result from the altered response of the individual end organ to a fundamentally constant metabolic disorder. In animals, the response of the vascular system to a sympathomimetic drug produces an individual reaction picture that is as characteristic as the finger print. The reaction picture of each animal is always identical provided the sympathomimetic stimulation is the same. So too in clinical pharmacology, the response of each patient to an injected sympathomimetic drug, such as adrenalin, is always identical and always individual. In clinical autonomic imbalance the "reaction picture" is individual and identical. The individual reaction picture in

clinical hyperthyroidism is the result not of differences in the deranged physiology but of the response of the individual tissue to a unitarian disorder. The practical importance of the unitarian concept dwells in management. If Plummer's hypotheses are accepted, the primary and secondary cases of hyperthyroidism must be managed differently both medically and surgically. If the unitarian concept is accepted, the management of all patients is identical. Iodides are never contraindicated and may be given to each patient with a reasonable prospect for a successful therapeutic result. The surgical procedure is never to be concerned solely with adenomatous nodules but is directed to the approach to subtotal removal of both tumor and non-tumor tissue.

Clinical Features

The obvious clinical features of hyperthyroidism need no special emphasis before this audience. A few characteristics warrant brief comment. Hyperthyroidism occurs most commonly in civilized society. It is frequently familial and is more common in women than in men, though men present the more severe manifestations of the disease. Professional and sedentary workers are more commonly afflicted than manual laborers. The disturbance occurs most often in early adult life when strife and tension are greatest. A disproportionate number of Jews are afflicted—a disparity which is also present in the incidence of diabetes mellitus. Focal infection, particularly in the upper respiratory passages and most commonly in the sinuses and tonsils, plays a dominant role in the initiation of exacerbations and occasionally in the production of toxic storms.

The hyperthyroid patients lack resistance both physically and mentally. They are prone to develop any current infectious disease. The combination of nervousness, asthenia and muscular dystrophy produces frequent accidents, and social stress and conflict.

Periarthritis of the shoulder joint, so-called "frozen shoulder," occurs with undue frequency. Manipulative treatment under anesthesia gives complete relief.

Clinical Course

Before the popularization of iodine therapy, Kessel and I^{53} studied the spontaneous course of hyperthyroidism in order that we might more accurately evaluate therapeutic procedures. The spontaneous

course of hyperthyroidism in the majority of patients is toward recovery. The remissions are interrupted by exacerbations. The spontaneous cycles of exacerbation and remission may be of greater or lesser severity. They may be brief or protracted. In a certain proportion of individuals, vital organ damage, either circulatory or hepatic,[54] will arise, terminating in chronic invalidism or death. Occasionally the dreaded thyrotoxic crises will be experienced[55]—a large proportion of these terminating fatally.

Complications

Mechanical symptoms arising from the pressure of the enlarged thyroid upon adjacent structures may complicate hyperthyroidism. Marked tracheal compression and distortion may occur without the production of subjective symptomatology. On the other hand, subjective complaints of dysphagia and dysphonia may be present, as the result of psychogenic factors (goiterophobia) with little or no objective evidence of pressure. In individuals who have had large goiters for many years, trachelomalacia may result. Trachelomalacia is a genuine surgical hazard. If its presence is suspected, the surgeon must be prepared to deal with tracheal collapse during the course of the thyroidectomy.

Malignant changes may occur in a goiter. Thyroid sarcomata are rarities. The diffusely hyperplastic gland rarely becomes carcinomatous. For the most part, carcinomata develop in adenomata. Statistics concerning the incidence of carcinomatous degeneration in adenomata vary according to the criteria of malignancy employed. Many of the histologic phenomena associated with malignancy may be observed in benign hyperplasia of the thyroid gland. If epithelial changes, without vessel invasion, be accepted as evidence of malignancy, then carcinoma of the thyroid is relatively frequent, reasonably benign and amenable to surgical therapy and irradiation. If the criteria of malignancy includes the phenomena of invasion of vascular structures, infiltration beyond the capsule or evidence of metastases, thyroid malignancy is relatively rare, highly malignant and therapy is all but futile.

Thyroid apoplexies may complicate hyperthyroidism. The rupture of an artery is uncommonly seen in diffusely hyerplastic glands but occurs more often in old cystic goiters with markedly sclerosed vessels. Thyroid apoplexy is one of the few painful thyroid afflictions. It is readily diagnosed, if suspected. Therapy may be expectant since the

thyroid capsule will act as a hemostatic.

Vital organ damage occurs in individuals with long standing hyperthyroidism. Marine[16] has called attention to the incidence of hepatic cirrhosis. Cardiac hypertrophy and dilatation with myocardial and coronary changes may develop. These may terminate in circulatory failure, producing the clinical picture of the thyrocardiac invalid.

The most characteristic and ominous complication is the acute crisis.[55] The thyrotoxic crisis consists in tempestuous exacerbation of all preëxistent symptoms and, in addition, a febrile reaction of non-inflammatory origin. The febrile reaction may be low grade or it may constitute an alarming and even fatal hyperpyrexia. Characteristic of the acute crises are the alarming tachycardias and paroxysmal cardiac irregularities. The neurological manifestations may consist either in agitation to the point of mania or collapse and coma.

The origin and explanation of these crises are even more obscure than those of hyperthyroidism itself. Crises may occur in individuals with mild evidences of hyperthyroidism, as well as those who are severely ill. I observed a crisis in a cretin. The crisis may occur without provocative cause; it may follow an acute emotional upset, an infection, or a surgical procedure, which need not necessarily involve the thyroid gland. The crisis may occur after an appendectomy or tonsillectomy, or the trauma of an accident. If the crisis follows thyroid surgery, the procedure may be one that is technically simple, as a ligation, or one of great magnitude, such as subtotal thyroidectomy. The thyroid crises are as unpredictable as they are violent. They constitute a constant threat in prognostication. Their incidence has been greatly reduced as the result of iodine therapy.

Management

The management of the individual patient with hyperthyroidism is a problem that has many facets. Each patient presents a unique situation, hence management must be individualized.

The constitutional autonomic imbalance that underlies the clinical picture of hyperthyroidism is not amenable to specific therapy. Preparations of belladonna, ergot and quinine have been suggested and employed. The use of belladonna is pharmacologically incorrect, since its paralyzant effect is upon the vagus rather than the thoraco-lumbar system. Quinine has no specific action on the involuntary nervous system. Though widely used, it serves no useful function. Ergot, and

more specifically ergotamine tartrate, is theoretically indicated. In practice, however, these drugs have been disappointing. We possess no modality that can successfully alter the tonicity of the thoraco-lumbar system.

The management of hyperthyroidism begins with the attempt to eliminate the factors that tend to precipitate exacerbation. The most important of these is psychic trauma. Commonly, the psychic insult is characterological or situational. It would be impracticable to summon a trained psychiatrist to aid in the solution of each clinical problem. Commonly the internist, or preferably the general practitioner, is aware of the psychic disturbance. A sympathetic understanding, patience and a desire to suggest social and familial adjustments will usually suffice to diminish the burden. The coöperation of the family, fellow workers or employers may be enlisted. General hygiene may be corrected so as to permit more rest. The friction of every day life may be diminished by kindly and thoughtful advice.

Where the psychic trauma is more deeply seated, the help of a trained psychiatrist is advisable, if not imperative. Psychiatric consultation should be postponed until the metabolic abnormality has been corrected.

Focal infection, as the excitant cause for exacerbations, must be judiciously managed. In the attempt to eradicate foci, particularly in the sinuses or tonsils, it should be remembered that the thyrotoxic crisis may be precipitated by operative interference anywhere in the body. Consequently, it is wise to postpone tonsillectomy, for example, until after thyroidectomy has been performed. If it becomes necessary, with the thyroid intact, to eradicate a focus, the same type of preoperative treatment as for thyroidectomy is to be employed.

The management of the catabolic excess includes both specific and non-specific therapeutic measures.

The non-specific management of the exacerbation requires removal of the patient from his environment and institutionalization in order to procure mental and physical relaxation. Except in the rarest of instances, where the home is so luxuriously equipped that complete isolation is possible, the patient with hyperthyroidism should be admitted for hospital care. Patients and friends, alike, protest against hospitalization and suggest compromises, such as rest at home or in the country, but these alternatives invariably fail for one reason or another.

A high calory, high vitamin diet is maintained in order to spare the

tissues from the ravages of the excessive catabolism. Sedative therapy by day and the hypnotics at night, assist in muting the nervous system.

Professional nursing care, at least during the day, is almost mandatory. An intelligent, sympathetic and cheerful nurse should be chosen. She should be taken into the confidence of the physician, particularly concerning situational difficulties that have given rise to conflict between patient and relatives. She may often tactfully manage the visitors who might otherwise be disturbing.

The patient must not be permitted to chafe through idleness. A daily schedule should be rigidly followed. This schedule may be completed by hydrotherapy, occupational therapy and visiting by appointment. A haphazard conduct of the sick-room will defeat the purpose of the rest cure. The radio, for example, may be used for a limited time. Under these circumstances it is quieting and sedative provided that amusing programs are chosen. If turned on casually and left on indefinitely, it becomes a nuisance.

For the specific management of the exacerbation, an infinite variety of therapeutic measures has been suggested. Many of these have previously been discussed. They include drugs such as belladonna, quinine and the ergots; glandular preparations such as thymus extract, adrenal cortical hormone; the principles of the male and female extracts such as estrone and testosterone and anterior pituitary extracts. None of these possesses any specific therapeutic value. Any improvement noted is probably a manifestation of the spontaneous remissions characteristically seen in the disease.

Roentgen therapy has been widely used for the control of the exacerbation. X-ray treatments of the thymic and anterior pituitary regions are certainly of no specific value. Irradiation of the thyroid gland has been employed by many workers, notably Means and Holmes,[56] and is still widely utilized. Hyperplasia of the thyroid gland is in no way altered by irradiation. Kessel and I could find no appreciable difference in the course of patients treated by "skillful neglect" and those who had been irradiated. Whatever benefits follow roentgen therapy of the thyroid gland result either from spontaneous remission or psychotherapy—the latter a potent non-specific factor in all types of physical therapy. If the x-ray therapy has any place in the management of hyperthyroidism, its use may be reserved for patients ineligible for thyroidectomy. If employed in those in whom thyroidectomy is

indicated, irradiation therapy, in my opinion, may be objectionable. The course of roentgen therapy delays the indicated operative procedure which then may be made technically more difficult by the increased fibrosis and vascularity of the irradiated tissue.

The re-discovery by Henry Plummer[57] of the amazingly specific effect of iodine in the treatment of hyperthyroidism constitutes one of the greatest of therapeutic achievements. Iodine may be given by mouth, inunction, injection or inhalation. The preparation may be organic or inorganic. The dosage is conventionally 5 to 10 drops of Lugol's solution three times a day. We are as ignorant of the correct dosage of iodine as we are of the mechanism by which the effect is obtained. Iodine should be given to every patient, whether of the so-called primary or secondary type, whether the thyroid gland is diffusely enlarged or adenomatous. The alleged contraindication to the use of iodine in so-called toxic adenomata has already been discussed. The specific effect of the drug is not dependent upon the histology of the thyroid gland.

Iodine therapy should be initiated immediately after the diagnosis is established. The response to the iodine may be used as a therapeutic test. If patients are to be institutionalized the drug should be withheld until the patient is admitted to the hospital lest the improvement lead to the belief that ambulatory therapy is possible.

The iodine reaction in hyperthyroidism consists in an extraordinary amelioration of symptoms. The effect may be measured by the diminution in the tachycardia and the fall of the basal metabolic rate. The relief of symptoms is initiated within twenty-four to forty-eight hours. Normality may be approached in two to ten days.

The immediate and dramatic therapeutic result does not occur in all patients. Occasionally the basal rate will be unaltered or it may actually increase. Many believe that these failures represented some altered reaction. The terms "iodine-fast"[58] and "iodine exacerbation"[59] have been employed to describe such instances. It is my own belief that the response to iodide in hyperthyroidism is always qualitatively the same. The quantitative differences depend upon the phase of the disease that is present during therapy. If the drug be administered at the onset of an exacerbation its effect will not be as obvious and dramatic as it would be if the patient were at the height of an exacerbation or at the beginning of a remission. The iodine effect is the sum of the specific action of the drug as modified by the violence of the exacerbation. If the patient fails

to improve with iodine therapy or the symptoms actually increase, not only should the drug not be stopped but increased dosage may be employed whilst further search is made for the continued operation of provocative exciting factors particularly in the psychogenic sphere.

The duration of iodine effect is variable and dependent mostly upon the underlying character of the disturbance in the particular patient. Many individuals with but slight evidences of hyperthyroidism may be more or less indefinitely maintained at normal by the continued use of the drug. Those, however, with moderate or severe hyperthyroidism whose spontaneous course is characterized by frequent and violent exacerbations may be held in a "compensated" state only long enough to permit them to be prepared for surgical procedure. Parenthetically, it may be stated here that the indications for operative interference should not be influenced by the iodine response. If surgical intervention is to be part of the therapeutic program a favorable iodine response must not alter the decision.

Limitation of the use of iodine to preoperative preparation is erroneously conceived, since many patients with mild disturbance may be carried along indefinitely by the use of the drug. The therapeutics of iodine in hyperthyroidism is a relatively simple problem that has been complicated by fanciful hypotheses, having to do with iodine fastness, iodine exacerbation, and allegedly qualitative differences in response where adenomata are present.

The mechanism by which the iodine effect is obtained is completely unknown. A priori, one would expect iodides to be contraindicated and, indeed, from the writings of Trousseau[60] to the notable contributions of David Marine[61] this viewpoint was current in medical practice. It remained for Marine to point the way for iodine therapy in hyperthyroidism and for Henry Plummer[4] to demonstrate its value practically and popularize its use.

While conservative therapy, including the use of iodine, will almost invariably produce a remission, exacerbations may be surely anticipated when the patient is returned to his normal environment and subjected to the stress and strain of existence.

Subtotal thyroidectomy offers the patient the quickest return to social and economic restitution and a minimal risk of later exacerbation. With the exception of relatively wealthy patients who can afford to be pampered and coddled over a long period of time, the mild cases

controlled by iodine and those individuals who are constitutionally opposed to surgery, it is my opinion that every patient with hyperthyroidism should be subjected to a thorough-going subtotal thyroidectomy.

The time to operate is to be determined by the clinical course. If the preoperative therapy succeeds in an approximation of the restoration to normal, no great time should be lost. Where circumstances will permit, I am in favor of the "stealing" operation. The time for operation should not be disclosed to the patient, so that the immediate panic and anxiety are allayed. Oftentimes the surgical procedure must be initiated earlier when very anxious and excitable patients become increasingly worse due to the suspense of the anticipated procedure.

Each patient should have some form of basal anesthetic. This may be avertin by rectal instillation or a barbiturate such as Nembutal taken orally. The use of an indifferent enema and lactose capsules for several days may mislead the patient from realizing the significance of the administration of the basal anesthetic.

The choice of anesthetic is a matter that can be determined by surgeon and anesthetist, but the decision as to the type of operation is one that must be settled between the surgeon and the internist or practitioner. The staged operation has the lower morbidity and mortality. It should be a matter of policy that if either surgeon or internist thinks the operation should be staged, the more radical opinion should yield to the conservative opinion.

The decision as to the staging of the procedure should not be made at the operating table and more surgery than originally planned must not be done merely because things seem to be going well. I favor the staged operation for patients whose original basal rate was greater than a +40 per cent; for those who have lost a great deal of weight and whose asthenia has been profound; for those whose basal rate cannot rapidly be brought to within twenty points of normal; for those who are highly agitated, nervous, restless; for individuals whose skins are deeply pigmented; for older patients with definite evidences of vital organ damage either in the liver or the circulatory system; for those who have a persistent hypertension or who have had any type of mental disorientation; for any patient who has ever had circulatory failure.

The first stage of operation should rarely be less than a hemithyroidectomy. If ligations are done the surgeon is faced with the alternative of multiple operations or a very formidable second stage

procedure. However, if the patient takes the anesthetic badly, if paroxysmal cardiac irregularity of an alarming degree develops, the operation must be stopped at whatever stage the difficulty may arise.

Postoperative treatment should be initiated in the operating theater or, at latest, immediately upon the patient's return to the bedroom. An intravenous drip of 5 per cent glucose in saline is to be started whether or not indications exist. After the first liter of fluid, the solution is changed to 5 per cent glucose in distilled water since it is unwise to overload the patient with salt. Iodine is to be given either directly into the drip; by rectum or, if the patient is coöperative, by mouth. Again, the dosage is difficult to estimate but it is common practice to use daily from ½ to 4 cc. of Lugol's solution for the first few postoperative days. The drip is to be maintained until the patient is wholly coöperative and well able to swallow fluids.

Many alarming complications may occur in the first few postoperative days. The most serious of these is the crisis with or without paroxysmal cardiac irregularity. Under these circumstances, there is invariably an elevation of temperature, as has previously been described. The vast majority of these postoperative crises are transitory and benign. Expectant treatment with sedatives or narcotics with continued intravenous administration of glucose and fluids will usually suffice. In the management of the postoperative crises, it is to be remembered that many patients with hyperthyroidism exhibit idiosyncrasy to morphine and that they are apt to vomit and become more agitated from the drug. The use of hypnotics such as the barbiturates and paraldehyde is considerably safer.

When the temperatures become excessive in the crises, that is beyond 104° F., antipyretic measures should be employed. These include sponges, packs, and the use of the coal tars. Kessel and I in instances of ominous thyrotoxic crises have used intravenous thyroxin in doses of 5 to 10 mgms. This has always been a measure of desperation, based on the possibility that the removal of the thyroid tissue produced some type of insufficiency in the metabolic economy. In a few instances, we have had the clinical impression that a specific result was obtained. This measure, however, is not to be employed unless the situation is ominous and the patient progressing unfavorably.

In the vast majority of instances, patients with crises are over-treated and may actually suffer from their medication. Digitalis is truly contra-

indicated, unless the patient has evidences of circulatory failure. Digitalis has no effect on the tachycardia of hyperthyroidism. If it is used merely because the pulse rate is rapid and the patient is in crisis, it can only be harmful, tending as it will to invite cardiac irregularity.

When the crisis takes the form of intractable vomiting or diarrhea, it may be necessary to use a continuous intravenous drip and basal anesthesia.

Purely surgical and mechanical complications such as hemorrhage, injury to the recurrent laryngeal, tracheal collapse or infection will be dealt with by those more competent to speak of these matters.

Complications will be more frequently encountered after subtotal thyroidectomy performed in one stage. If the partial operation has been performed, an interval must elapse before the completion of the subtotal thyroidectomy. In convalescence after the complete operation or between the staged operations, the patient is to be permitted to sit up, and get up out of bed, as soon as the wound stitches have been removed and the temperature and pulse rate are normal. A soft and then full diet is to be advised immediately. We see no reason to wait more than ten days or two weeks between operative stages unless the condition of the patient makes it seem wise to temporize. Where patients are in fine condition, waiting excessively long periods such as three to six months means that the patient must be discharged from the hospital only to be readmitted. The suspense and strain are not warranted by any possible advantage over the shorter wait. If the second stage is done within ten days or two weeks, the patient may be kept at the hospital. The preparation for the second operation includes a return to the routine that preceded the first operation, including the use of iodine.

After the subtotal thyroidectomy has been completed, the internist again resumes complete charge of his patient. Iodine is continued in decreasing dosage for a long period of time in order to prevent hyperplasia of the thyroid remnant. The daily dose may be reduced to 20—10—then 5 drops of Lugol's solution, and later need be given only 5—4—and 3 days a week. In the female, the administration of iodine should always be employed at the menstrual time.

The patient must not attempt to resume a normal existence upon discharge from the hospital. If possible, there should be a period of convalescence, preferably in the country. The restfulness and peace of mountain quiet for this purpose is superior to the more stimulating

atmosphere of the seashore. Upon return from convalescence, the physician should discuss the patient's way of life in great detail, both with patient and family. Care must be taken that the physical and mental resources are not again strained. Rest periods should be interspersed in the course of the day or upon return from work; the week-end should be used for convalescence and one day might well be spent in bed. The use of sedatives and hypnotics is to be continued and the basal rate must be followed. When the subtotal thyroidectomy is adequate, the majority of patients exhibit a low basal metabolic rate at the end of a few weeks or months. If there are no associated conditions, the patient need not be treated with thyroid extract. If, however, the patient develops evidences of cachexia strumipriva, thyroid extract should be given in sufficient doses to bring the basal rate to approximately −10 per cent at which level the subjective symptoms should disappear. At this point a maintenance dose of thyroid extract must be worked out lest the continued use of the corrective dose lead to poisoning. The corrective and maintenance dose of thyroid cannot be prescribed a priori. Usually these postoperative patients will need more than the expected dose. There is no advantage in using thyroxin intravenously or by mouth in preference to a good crude thyroid extract.

The prognosis in hyperthyroidism today is universally bright, thanks to Plummer's popularization of iodine and the amazing skill of our operating surgeons. Whereas, 25 years ago, in the pre-Lugol days, we faced a surgical mortality approximating 15 to 20 per cent, today, a single operative death in a large series is a calamity that demands explanation. This optimistic viewpoint must not be interpreted by general surgeons to indicate that the operative therapy of hyperthyroidism is lightly to be approached. The procedure, though technically simple, is too treacherous and dangerous to be attempted by the average surgeon who does an occasional operation. A medical wag once stated the problem sagely when he said that no man should do a subtotal thyroidectomy until he has done a hundred. No surgeon, however competent, should attempt the management of these patients without the assistance and coöperation of an experienced practitioner or internist. If there is any problem in the field of medicine that requires team work and coöperation, it is the management of the patient with hyperthyroidism. We, in America, may point with pride to our leadership in the solution of the problems raised in the therapy of hyperthyroidism.

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HYPERPARATHYROIDISM*

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Evolution of the Concept and Definition of Hyperparathyroidism: It is now almost fifteen years since a case of Recklinghausen's bone disease was treated for the first time on the supposition that it might be based upon parathyroid hyperfunction. The surgical history of this case is both illuminating and somewhat ironic, as will be indicated later on. At any rate, the dramatic though temporary improvement which Mandl[1] obtained by removing a parathyroid adenoma from the subject in this case turned out to represent the cue to a significant clinical advance. It is true that pathologists[2] had already noted the common presence of a parathyroid adenoma in cases of so-called "generalized osteitis fibrosa cystica" of Recklinghausen. However, they had not hitherto fully grasped the pertinent causal connection between the skeletal alterations and the parathyroid lesion.

The aforementioned clinical advance was concomitant with the development, by Hanson[3] and by Collip,[4] of chemical methods for the preparation of potent parathyroid extracts. The experimental approach to the question of parathyroid hyperfunction thus also became possible. Collip found that by injection of his extract (parathormone) he could raise the serum calcium level of normal dogs. He was further able to prevent the onset of, or abolish, in dogs, the hypocalcemia and tetany of parathyroprivia—manifestations first interrelated by MacCallum and Voegtlin[5] in 1909. In addition, Greenwald and Gross[6] found that in dogs the hypercalcemia caused by parathormone was associated with an increased excretion of calcium and phosphorus through the urine. Furthermore, Albright and his colleagues[7] demonstrated that the effects of the injection of parathormone in man were similar to those in dogs. In regard to the blood, they noted that small doses of parathormone depressed the inorganic phosphate level, and raised the calcium level, of the serum.

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In collaboration with Bodansky and Blair,[8] I was able to show in addition that in various susceptible animals the repeated injection of parathyroid extract induces bone lesions analogous in many respects to those seen in Recklinghausen's disease.

Meanwhile, cases confirming the dramatically beneficial effects of removal of a parathyroid adenoma in this disease were accumulating from many sources.[9] The cases in question also showed that, like the experimental injection of parathyroid extract, in dogs and human subjects, the disease tends to be associated with a rise in serum calcium, a drop in the inorganic serum phosphate, and an increased excretion of calcium and phosphorus in the urine. Altogether, then, by about 1931, the principal links in the chain of evidence for the idea that Recklinghausen's disease of bone is based upon parathyroid hyperfunction had been forged and connected.

The demonstration of this causal relationship between Recklinghausen's disease and an offending parathyroid adenoma finally destroyed the already waning theory of Erdheim,[10] that parathyroid enlargement appearing in association with bone disease should be regarded as secondary to, and compensatory for, the bone changes. On the basis of the Erdheim hypothesis, Mandl himself, in the case which later became classic, resorted at first to homoplastic parathyroid transplantation. However, when he found that the condition of the subject was aggravated by this procedure, he used the opposite one of searching for, and removing, the enlarged parathyroid known usually to be present in these cases. Nevertheless, though the Erdheim theory has had to be abandoned, we should not forget that Erdheim was a pioneer in appreciating the importance of parathyroid-skeletal interrelationships.

Guided especially by the recent work of Castleman and Mallory,[11] the present tendency is to classify parathyroid enlargement in general as taking the form of either a neoplasia or a hyperplasia. Parathyroid neoplasia, which is relatively uncommon, usually affects a single gland, though occasional instances of tumorous or neoplastic enlargement of two glands have been encountered. Parathyroid hyperplasia affects all (that is, the theoretical four) parathyroids. Even if one or two of the glands are not grossly enlarged, they at least show microscopic evidences of hyperplasia. Parathyroid hyperplasia has been subdivided into primary (or idiopathic) and secondary hyperplasia. This division is made on the basis of absence or presence, respectively, of some plausible

instigating factor, and also on the basis of certain differences in histologic detail. In Recklinghausen's disease of bone, the parathyroid disorder is usually a neoplasia, though occasionally an idiopathic hyperplasia.

Secondary parathyroid hyperplasia is encountered not infrequently in rickets and osteomalacia and sometimes also in Paget's disease of bone, carcinoma extensively metastatic to the skeleton, multiple myeloma, Cushing's syndrome, etc. It is commonly found in cases of chronic renal insufficiency. In fact, secondary parathyroid hyperplasia is found more regularly, and is more pronounced on the whole, in connection with chronic renal insufficiency than with any other condition in which it has been reported.

It is the clinico-pathologic effects of parathyroid hyperfunctioning that represent what we shall mean by hyperparathyroidism. It is the pathology, the clinical aspects, and the differential diagnosis of hyperparathyroidism arising in association with neoplastic or idiopathic diffuse parathyroid enlargement that will mainly concern us for the rest of this paper. Since we do not know what instigates the parathyroid hyperfunctioning in these cases, we can think of them as instances of primary hyperparathyroidism. The question also arises whether, in cases manifesting secondary parathyroid hyperplasia, parathyroid hyperfunction ever becomes severe enough to induce pronounced skeletal and other tissue changes in its turn. The answer to this question seems to be in the affirmative, notably in connection with long-standing chronic renal insufficiency associated with pronounced parathyroid hyperplasia secondary to the renal disease. Indeed, recent observations have established unequivocally the existence of an important kidney-parathyroid interrelationship. The hyperparathyroidism appearing under such conditions may be regarded as a complicating or secondary hyperparathyroidism.

Incidence: Primary hyperparathyroidism, while not a common disease, is not rare. Its incidence seems to be at least two or three times as high among females as among males. It occurs most frequently between the ages of 30 and 60. While it is not uncommon at other ages also (notably between 20 and 30 years), it seems to be definitely rare below 10 years. No racial, hereditary, dietary, or environmental factors in the incidence of the disease have been definitely established. However, it seems worth noting in this connection that Goldman and Smyth[12] do report two cases appearing in the same family, one in a girl of 17 and the other in her brother of 23. Also, I have the impression

that the disease used to be more common 20 or 30 years ago than it is now, albeit it was then often misdiagnosed as osteomalacia, or senile osteoporosis or osteomalacia. I have gained this impression from study of the pathologic material and notes of the late Professor Erdheim,* having found such cases particularly abundant for this earlier period. The material also shows that when female subjects suffering from the disease became pregnant, the disease was strongly aggravated.

Course of the Disease: The onset of the disease is usually insidious and its course protracted. The subjects are likely to complain early of vague, aching pains, especially in the limbs, and of stiffness in joints. The clinical manifestations may be misinterpreted for months or years. Indeed, the presence of the disease is sometimes not suspected until the dramatic fact of a pathologic fracture leads to the diagnosis. The way to the latter is also sometimes first opened up through the discovery of a bone swelling. Indeed, I personally have seen two cases in which dentists had made the proper association between a so-called giant-cell tumor of a jaw bone and an existing hyperparathyroidism. Furthermore, there are many cases in which renal symptoms, and notably those of renal calculus, are the presenting ones and the skeletal alterations are in the background or even equivocal. Occasionally, gastrointestinal symptoms such as attacks of nausea and vomiting are prominent and even the presenting phenomena, if the skeletal alterations are not clinically obvious, may confuse the clinician as to the true nature of the condition.

Unless the offending parathyroid tissue is removed, the disease usually progresses until the patient is hopelessly bed-ridden in consequence of pain, repeated fractures, and deformities (Figs. 1, 2). There is wide variation in the speed with which this course is run. In one of the cases which I studied from the Erdheim material it was completed in eight months, while in another it was completed in three years. However, even three years represents a relatively short course, for many cases seen today in which the patients are not yet badly deformed already have a relevant history dating back longer than this. Fortunately, the

* This is the personal material willed by the late pathologist, Professor Jakob Erdheim of Vienna, to his former assistant and friend, the late Dr. Ernst Freund, more recently of Los Angeles, and brought to this country by Dr. Philipp Rezek, now of Miami, Florida. It was bequeathed by Dr. Freund to me, and I am now having it established at the Hospital for Joint Diseases as a museum to the memory of Professor Erdheim. I wish to acknowledge this collection as the source of some of the pathologic material used in connection with this lecture.

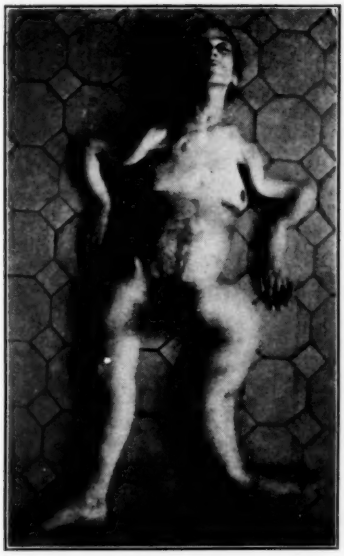

Fig. 1—Photograph of cadaver of 32-year-old woman, revealing devastation of the skeleton in connection with hyperparathyroidism. Death occurred in 1925, a year which represents a transition in our understanding of the disease toward the prevention of such severe skeletal involvement.

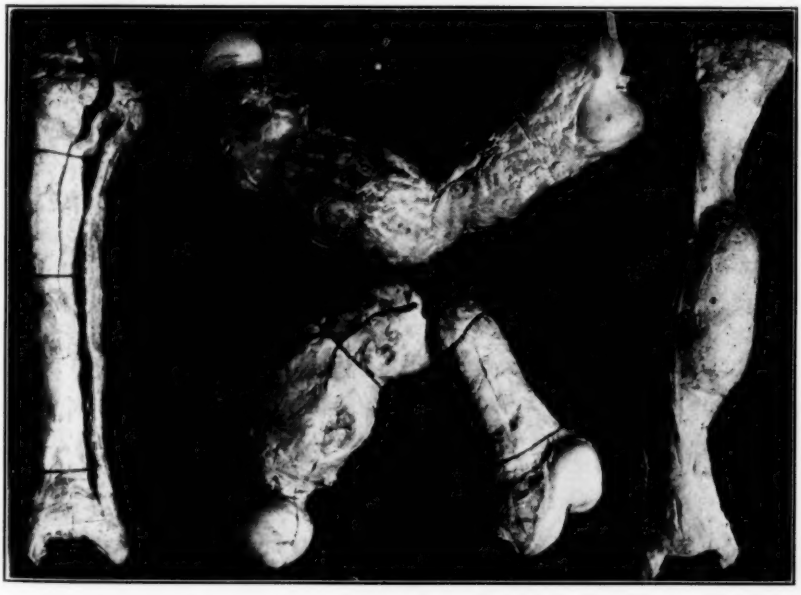

Fig. 2—Photograph of the long bones removed from the lower limbs of patient shown above, in this case emphasizing their extreme curvature and irregular distension.

condition is now usually properly diagnosed and treated before it has advanced enough really to devastate the skeleton. If the condition is allowed to go unchecked, death ensues, usually in consequence either of uremia or of an intercurrent disease such as pneumonia.

General Pathology of the Skeletal Changes: More and more frequently, we now encounter clinical cases of hyperparathyroidism in which, even roentgenographically, there is still little if any evidence of skeletal involvement. These cases are picked up at this early stage because observers are now alert for the disease and because there are now established laboratory criteria for its diagnosis. Formerly, such cases were picked up only incidentally at autopsy, the subjects having died from some other cause. In cases of hyperparathyroidism with minimal skeletal involvement, the gross changes so far as the bones are concerned may consist merely of a slight porousness of the vertebral column, ribs, pelvis, and long bones.

Microscopically, in these cases with very slight skeletal changes, the bones show merely a mild degree of generalized osteoporosis and fibrosis. This stands out more clearly in some bones—notably the ribs, the femora, the jaw bones, and the bones of the vertebral column—than in others such as the bones of the hands and feet. The spongy trabeculae of the affected bones are found perforated by, and surrounded by, tracts of connective tissue (Fig. 3). The cortices of these bones show enlarged vessel canals containing abnormal amounts of connective tissue. On the walls of the trabeculae and vessel canals where the resorption has been going on, osteoclasts and Howship's lacunae are in evidence. In these cases, little if any new bone has yet appeared in the connective tissue that is replacing the original osseous tissue.

Progression of the disease in the skeleton is characterized by increasing resorption of the original osseous tissue and increasing replacement of it by connective tissue in which new bone is formed. However, the substitute bone, which is rather primitive histologically, tends to remain moderate in amount and not to be particularly rich in calcium. Eventually, in a severely affected bone, the internal architecture shows extensive modification and there may no longer be any vestige of original osseous tissue.

This status is approached through broadening and thickening, followed by merging of the tracts of connective tissue surrounding and replacing the spongy trabeculae (Fig. 4). In this way, large fibrous scars

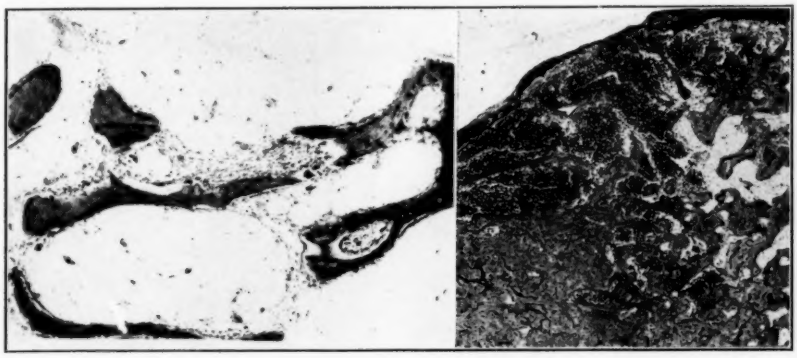

Figure 3 Figure 4

Fig. 3—Photomicrograph x125 from an early case showing dissection and perforation of the original trabeculae at the end of a long bone by tracts of connective tissue. Much of the intertrabecular marrow is still fatty, and as yet there is little if any evidence of new bone formation in the substituting connective tissue.

Fig. 4—Photomicrograph x6 from an advanced case, showing substantial replacement of the spongiosa at an end of a long bone by connective tissue and new bone which, in the lower left hand corner, can be seen to have formed a rather dense scar.

are formed in the place of the original spongiosa. Though connective tissue and new bone substantially or completely replace the original cortical bone, too, reactive periosteal new bone deposition is lacking except at sites of fracture. The cortical thickening which one occasionally encounters in a bone even without fracture can be shown to have taken place on its medullary side. In the transformed cortex and spongiosa one may encounter small or larger brownish fibrous scars representing the so-called brown or giant-cell tumors. Smaller or larger cysts may also be found, but these are by no means as common anatomically in hyperparathyroidism as the synonym, "generalized osteitis fibrosa cystica," would imply (Fig. 5). In very severe cases, fractures, and the consequences which they entail in the form of hemorrhage, reactive callus formation, and malalignment complicate and confuse the anatomic picture in the different bones.

As to the distribution of the skeletal lesions, one would expect that since the action of parathyroid hormone upon the osseous system occurs through the blood stream and circulating tissue fluid, the bones would be evenly affected. As a matter of fact, in any given case, all do show involvement to some extent. They are by no means evenly affected,

Figure 5

Figure 6

Fig. 5—Photograph of humerus of a 19-year-old girl who had suffered from hyperparathyroidism. The deformity at the head-shaft junction developed at the site of a fracture. The major marrow cavity is intact and contains myeloid and fatty marrow. The shaft cortex is completely transformed. At A, the cortex is occupied almost throughout its thickness by a "brown" tumor.

Fig. 6—Photomicrograph x6 showing, on a larger scale, part of the brown tumor and cortex above it from the humerus pictured in Fig. 5.

however. On the whole, it is those bones and bone regions which are subjected to the strongest functional stress and strain that are the most likely to be seriously implicated in hyperparathyroidism. The tendency toward pronounced involvement of the long tubular bones and the vertebral column, for example, becomes understandable on this basis. Nevertheless, there may be discrepancies, in the degree of involvement, between two bones (such as the femora) which, in theory, would be expected to be equally implicated. Such differences may logically be

attributed to the presence of special complicating factors such as infractions or fractures, or the favoring of one side at the expense of another in such a way that the latter would be more likely to develop pronounced lesions. The importance of functional trauma in the localization of the skeletal lesions is especially striking in the case of the terminal phalanges, which, in contrast to the middle and basal phalanges, are likely to undergo particularly severe changes leading to clubbed fingers.

Even when the skeletal lesions are far advanced, the fully developed erupted teeth do not become involved in the general decalcification, although they may fall out in consequence of involvement of the jaw bones. Indeed, as Thoma[13] has shown, these teeth may even be hypercalcified. The developing teeth in man tend to show pronounced defects in dentin formation. In conformity with this finding, Schour and Ham[14] noted that in rats suffering from acute hyperparathyroidism the newly forming dentin of the incisor teeth may show deficient calcification.

Cysts and Brown Tumors: The nature and pathogenesis of these lesions, and their significance in the total skeletal picture of hyperparathyroidism present very complex problems. Anatomically, gross cysts and tumors are much less frequently encountered than the generally prevalent concept of the disease would lead one to expect. It is true that even in relatively early cases the bones may show cyst-like shadows roentgenographically. However, there is no proof that these shadows do not represent merely fibrous foci which have caused defects in the cortex or in the spongiosa and cast cyst-like shadows without actually being cysts. Indeed, this can be deduced from general experience with solitary bone lesions casting shadows suggesting cysts. On surgical exploration, these shadows very often turn out to represent merely areas of cortex or spongiosa which have undergone partial or complete replacement by cartilage, by fibrous tissue, by granulomatous tissue, etc. Furthermore, it is difficult to state with certainty how cysts form when they do form in cases of hyperparathyroidism. It seems likely that the majority of them represent merely fibrous masses or brown tumors which have undergone cystic degeneration after ischemia or hemorrhage.

The problem of the brown tumor in hyperparathyroidism is even more perplexing than that of the cyst. The impression which one obtains from the literature is that this lesion is more or less the exact counterpart of the solitary giant-cell tumor of bone. Our own findings are not in harmony, on the whole, with this conception. First of all, it

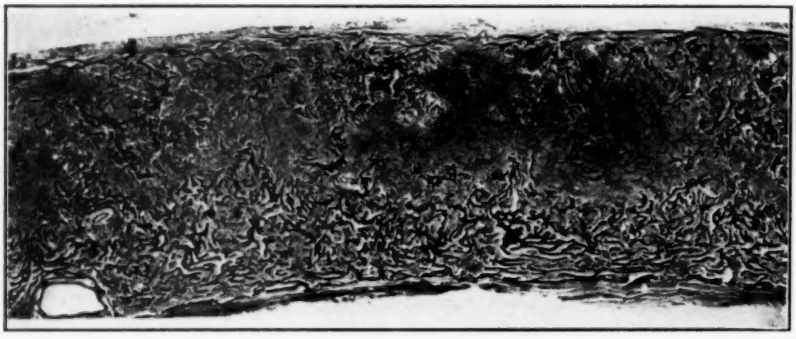

Fig. 7—Photomicrograph x6 of a rather completely transformed calvarium showing, in the upper part of the picture, a large fibrotic area which, in the gross, appeared brownish and which represents a so-called brown tumor.

seems clear that the histologic criteria for the diagnosis of solitary giant-cell tumor of bone ought to be kept much narrower than they are. The tendency to label as a giant-cell tumor any fibrous lesion or scar in bone which contains a few osteoclasts is to be deplored. It is this loose labeling that is responsible for the inclusion, in classifications of bone tumors, of such categories as "the osteitis fibrosa variant of giant-cell tumor" and "the giant-cell variant of osteitis fibrosa."[15] Strictly defined, a solitary giant-cell tumor of bone is a true neoplasm which originates from mesenchymal connective tissue and in which the stromal cells and the giant cells show a close histogenetic relationship. Furthermore, in such a tumor, one should be able to see evidence that the giant cells are being formed from the stromal cells and also that the giant cells are abundant, are a significant part of the histologic picture, and do not resemble ordinary osteoclasts.

The brown tumors of hyperparathyroidism usually do not meet these criteria (Figs. 7, 8). In them, as a rule, the giant cells are relatively sparse and quite closely resemble the osteoclasts present beyond their immediate area. Altogether, the brown tumors in hyperparathyroidism seem to represent small or larger fibrous scars containing some osteoclasts. However, the strict interpretation of them in this way encounters an obstacle. This is represented by the conditions obtaining when a brown tumor of a jaw bone irrupts under the gum in the form of an epulis. In these cases, for some obscure reason, the histology of

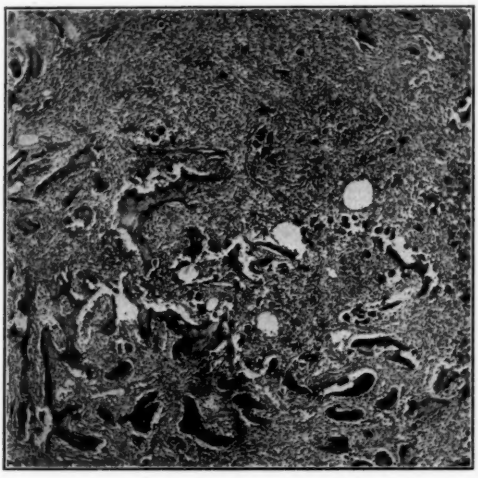

Fig. 8—Photomicrograph x100 showing the details at the periphery of the lesion. The fibrous stroma and giant cells of the brown tumor area are not essentially different from these elements in the neighboring tissue.

the lesion under the gum resembles that of solitary giant-cell tumor more closely than that of a brown tumor elsewhere in the bones in hyperparathyroidism. Through the courtesy of Dr. Blum and Dr. Gettinger, I have had occasion to examine pertinent tissue from the gum and jaw bone in two known cases of hyperparathyroidism with jaw involvement. In these cases, though the cytology of the epulis lesion resembled that of solitary giant-cell tumor, it appeared to me that that part of the brown tumor located in the jaw proper still retained some of the features of a fibrous scar with osteoclasts. It is difficult to understand why epulids in hyperparathyroidism should thus bear a special resemblance to solitary giant-cell tumors. Possibly it has something to do with functional trauma and hemorrhage into the lesion. Possibly also, even outside of jaw regions, such factors may have a similar influence upon a brown tumor. We can only say that our own material showed nothing of this kind.

Pathology of the Extra-Skeletal Changes: As has already been noted, the parathyroid abnormality in hyperparathyroidism may be of the

nature of an adenoma or of a hyperplasia. When the abnormality is adenoma formation, the tumorous growth is usually limited to a single gland. As often as not, the adenoma is composed almost solely of typical chief cells, and when it is not, it still contains some chief cells. When the abnormality is a hyperplasia, it involves the theoretical four glands, and the hyperplastic glands are composed of water-clear cells.

Aside from the parathyroids, the kidneys are the extra-skeletal tissues most likely to be affected in hyperparathyroidism. Indeed, with the parathyroid disorder as the apex of the pathologic triangle, the two important sides of it are skeletal lesions and renal lesions. Of the latter, renal calculi are among the commonest. Somewhat more than one-third of the cases of hyperparathyroidism presenting roentgenographic evidence of bone lesions also show renal calculi. Furthermore, the incidence of renal calculi is even higher if one includes cases of hyperparathyroidism which as yet do not show clear-cut roentgenographic evidence of skeletal involvement. For these reasons, determination of the serum calcium seems clearly indicated in all cases of renal calculus, and if this value is found above normal the skeleton should also be roentgenographed.

Nephrocalcinosis is another important, though much less common, renal complication, and may appear independently or in association with calculi. The calcium deposition is mainly peritubular and is likely to obstruct the tubules and interfere with their function. Kidneys damaged by the presence of calculi or nephrocalcinosis may also show evidence of superimposed infection in the form of pyelonephritis. Altogether, chronic renal insufficiency is very likely to appear. This in its turn probably increases the parathyroid hyperfunction and hence exacerbates the state of hyperparathyroidism. If the kidneys have been damaged irrevocably, the chronic renal insufficiency may exert its effects upon the parathyroid glands remaining after removal of an adenoma. Especially in cases with severe renal insufficiency, widespread metastatic calcifications may be present in many soft parts, including the subcutaneous tissues and arteries.

Differential Diagnosis: A number of conditions may present problems of differential diagnosis in relation to hyperparathyroidism. It is immediately helpful to remember that the latter disease is, after all, relatively uncommon. Because of this fact, in weighing whether a given obscure case is or is not one of hyperparathyroidism, the burden of

proof lies upon the affirmative side. The conditions whose manifestations sometimes raise this problem of differential diagnosis include: adolescent rickets and osteomalacia, senile osteoporosis, carcinoma extensively metastatic to the skeleton, multiple myeloma, Paget's disease, and polyostotic fibrous dysplasia.

Before proceeding with the discussion of differential diagnosis, it seems advisable to consider the question of protracted renal insufficiency. In the latter condition, both in childhood and in adult life, hyperparathyroidism may be present as a complicating or secondary disorder even if renal disease is the underlying one. The pronounced osseous changes occurring in cases of renal rickets are well known and have been adequately described. In fact, solely on the basis of histologic study of bone sections, it is usually not possible to tell whether one is dealing with a case of renal rickets or one of hyperparathyroidism. It is true that in the former condition one does not see the brown tumors and cysts, but these are not necessarily to be found in hyperparathyroidism either. Extensive osseous changes have also been observed in a few cases of chronic renal insufficiency in adults, in which they have usually been denoted as generalized osteitis fibrosa. In these cases there was pronounced enlargement of the parathyroids, such as one sees also in cases of renal rickets. Altogether, the osseous findings in these cases may be regarded as the adult equivalent of those noted in renal rickets of childhood. In the presence of such pronounced osseous changes, secondary hyperparathyroidism can safely be inculpated as a factor contributing to the causation of the bone lesions. Anderson[16] has recently reviewed the whole question of hyperparathyroidism in relation to renal disease.

Of further interest in regard to the relation of chronic renal insufficiency to the osseous system are certain findings which were recently noted by my former associate, Dr. Ginzler, and myself.[17] In the usual run of cases of chronic renal insufficiency revealing mild degrees of parathyroid hyperplasia at autopsy, we have routinely examined bones from various parts of the body. Our observations in regard to these cases may be summarized as follows: The bones, though usually not altered grossly, often reveal, on microscopic examination, mild but clear-cut fibroporotic changes in the spongiosa. In these cases, the spongy trabeculae show scattered resorption lacunae containing osteoclasts and connective tissue, and some of them may also present, here and there, deposits of new bone. Occasionally—and specifically when the renal

insufficiency has been very protracted—the bones will be found even grossly altered. In these cases, the spongiosa is close-meshed, and the trabeculae are thickened and distorted, so that altogether the skeletal condition amounts to an osteosclerosis. The microscopic observations indicate that the osteosclerosis has developed through gradual accretion of new bone, despite the alternation of reparative with resorptive processes that must have been going on for a long time.

Only Rutishauser[18] has described osseous changes sometimes rising to the level of osteosclerosis in patients with renal disease in whom secondary hyperparathyroidism was probably a factor, though only a subordinate one, in the development of the bone lesions. What probably underlies most of the bone changes in these cases is the chronic acidosis due to the renal damage.

We turn now to adolescent rickets and osteomalacia. We all know that adolescent rickets is by no means as common in the United States at present as it was thirty or even ten years ago. In fact, at our hospital, despite the high proportion of negroes in its ward and out-patient population, we practically no longer see cases of adolescent rickets. In the rare instances in which hyperparathyroidism appears in children, it may be mistaken for adolescent rickets. This is so because, like rickets, it tends to lead to generalized demineralization of the skeleton, widening of the epidiaphysial regions, deformation of the thoracic cage, coxa vara, and knock knees or bow legs. However, in view of the rarity of both genuine adolescent rickets and hyperparathyroidism, children now found presenting these skeletal abnormalities are more likely to be suffering from so-called renal rickets or idiopathic steatorrhea than from either of the other two disorders. Serum calcium and phosphorus determinations of course aid in the differential diagnosis. In cases of idiopathic steatorrhea the gastrointestinal history also sheds light. Furthermore, in cases of adolescent rickets, renal rickets, and idiopathic steatorrhea one does not find such roentgenographic bone shadows as would indicate the presence of cysts and so-called "brown tumors."

Genuine osteomalacia of adults—that is, the osteomalacia of calcium deprivation and added vitamin D deficiency—has always been rare in this country. This is the osteomalacia which is associated with repeated pregnancy or pregnancy of young girls and which is still endemic in parts of China and India. Occasionally, in this country, we do encounter a sporadic instance of non-puerperal bone softening which simulates genuine

osteomalacia but does not respond to the usual treatment for this condition. At any rate, in cases of osteomalacia, as contrasted with hyperparathyroidism, the serum calcium value is at most, barely up to the normal and is usually subnormal. Furthermore, in osteomalacia, the roentgenographs of the skeleton do not reveal the cysts and "brown tumors" not uncommon in hyperparathyroidism, nor are the bones usually as much rarefied as they are in an advanced case of hyperparathyroidism. In their general tenor, these remarks are true also in relation to nutritional and hunger osteoporosis.

Occasionally, senile osteoporosis, too, is mistaken for hyperparathyroidism. It may be worth mentioning, however, that I have seen definitely fewer instances of senile osteoporosis in recent years than I formerly saw. This fact seems to reflect the recent advances in our knowledge about nutrition, and the raised standards of care for the old. Of considerable aid in the differential diagnosis is the fact that in senile osteoporosis the serum calcium, phosphorus, and phosphatase activity values are normal unless fractures are present. In the presence of the latter, the phosphatase activity value may be found elevated but not, of course, the serum calcium value.

Cancer extensively metastatic to the skeleton sometimes also raises the problem of differential diagnosis, although confusion on this point can be easily avoided. The diagnostic difficulty is most likely to appear if, as happens in rare, extreme cases, the metastatic bone involvement is associated with a hypercalcemia. In any event, even if the primary growth is not clinically evident, there is one roentgenographic feature which can prevent the diagnostic error. This is the fact that in cancer, no matter how extensive the rarefaction of certain bones may be, or how strongly their appearance may suggest Recklinghausen's disease, other bones, and sometimes even parts of badly affected bones, will be found relatively normal roentgenographically. In Recklinghausen's disease, on the other hand, when some bones are badly affected, all the rest will be found at least somewhat altered.

Not infrequently, indeed, I have observed cases of multiple myeloma which have been misinterpreted, at least temporarily, as instances of hyperparathyroidism. I suppose it is the relatively common finding of a hypercalcemia in multiple myeloma that is at the bottom of this confusion. However, in the presence of this finding, further investigation of the blood will reveal a hyperproteinemia with an inversion of the

albumin-globulin ratio. The latter finding should be immediately recognized as the cue to the presence of multiple myeloma. Furthermore, multiple myeloma is characterized by the fact that the serum phosphatase activity tends to remain normal, no matter how extensive the skeletal involvement may be. It is conceivable that if the serum phosphatase activity is measured at a time when numerous fractures are in the process of healing, this activity may be found slightly increased, but the increase does not attain the level that it usually shows in advanced cases of hyperparathyroidism. In addition, it is well known that a good percentage of cases of multiple myeloma also show, sooner or later, a Bence-Jones proteinuria.

Actually, a proper appreciation of the roentgenographic appearance of the calvarium in cases of multiple myeloma should suffice to prevent confusion with hyperparathyroidism, irrespective of the roentgenographic findings elsewhere. The small punched-out areas of rarefaction in the calvarium are rather typical for multiple myeloma and are not found in hyperparathyroidism. The rarefactions of the calvarium in Hand-Schüller-Christian's disease are usually much less numerous and much larger. The so-called circumscribed osteoporosis of the calvarium found early in involvement of the skull in Paget's disease is also easily distinguishable, on the basis of the small number and large size of the rarefactions, from cranial involvement in multiple myeloma. Finally, reference should be made to the hyperplastic parathyroids sometimes to be found at autopsy in cases of multiple myeloma. I am inclined to think that the hyperplasia in these cases is secondary to the renal insufficiency so often developing in the course of the disease.

Paget's disease should no longer ever be confused with Recklinghausen's. The total picture—clinical, biochemical, and roentgenographic—is clearly different. The pathologico-anatomic picture is also decidedly different. One does not find, in hyperparathyroidism, the large circumscribed areas of rarefaction of the calvarium that are characteristic of the early stages of Paget's disease of the skull. In uncomplicated cases of Paget's disease the serum calcium and phosphorus values are normal. However, very rarely, one encounters a case of Paget's disease in which routine biochemical study reveals a definite hypercalcemia. A few cases of this type have been subjected to exploration of the neck for a parathyroid adenoma, which indeed was found. However, in these cases, the extirpation of the adenoma did not influence the course of the Paget's

disease. These cases must be interpreted as instances of Paget's disease complicated by hyperparathyroidism, or at least as instances of the coexistence of the two diseases in the same subject.

A condition which is frequently and unnecessarily misdiagnosed as hyperparathyroidism is "polyostotic fibrous dysplasia," which my colleague and associate, Dr. Lichtenstein,[19] named and recently described in detail, emphasizing especially its pathology. Clinical reference to the condition had previously been made under such names as "unilateral fibrous osteodystrophy," "unilateral Recklinghausen's disease," "disseminated osteitis fibrosa," "osteitis fibrosa in multiple foci," etc.

The condition is a skeletal developmental anomaly affecting several or many bones, with predominantly unilateral involvement. The affected bones show filling of their medullary cavities by gritty, grayish-white fibrous tissue containing trabeculae of newly formed primitive bone. Islands of cartilage may also be found in the fibrous tissue filling the marrow cavity. The condition apparently results from perverted activity of the specific bone-forming mesenchyme. It usually manifests itself in childhood or early adult life and evolves slowly, pursuing a protracted clinical course characterized by pain, deformity, and a tendency to pathologic fracture of affected bones. Precocious menstruation in girls suffering from severe forms of the disease has been described by Goldhamer,[20] by Borak and Doll,[21] and more recently by Albright and associates.[22] The presence of hyperpigmentation of certain areas of the skin, apparently due to excessive melanin content, has also been mentioned by Goldhamer and particularly stressed by Albright and his associates. The precocious menstruation and hyperpigmentation are apparently seen only in very severe cases whose clinical manifestations have begun very early in life.

It is probable that the precocious menstruation and other endocrine phenomena, manifested in only a small proportion of these cases, result from damage to structures at the base of the brain from involvement of underlying skull bones. Indeed, one exhibitor at this Fortnight is demonstrating several of these special cases under the heading of: "A rare Endocrinopathy probably of Pituitary-Hypothalamic Origin." Another is showing a number of them under the heading of: "A Syndrome characterized by Precocity in Females, Hyperpigmentation, and disseminated Osteitis Fibrosa." All these cases would fall into their proper place as instances of particularly severe polyostotic fibrous dysplasia with sec-

ondary phenomena due to damage of the base of the brain and possibly nerves. One should bear in mind that the great majority of cases of this disease show no such secondary phenomena and that indeed even the osseous changes may be limited to a few bones developing from a single limb bud.

It is because roentgenographically the affected bones appear widened, show thinned cortices, and often present appearances suggesting the presence of cysts that these cases are so often misinterpreted as instances of hyperparathyroidism. At least five or six cases of the seventeen which have come under my personal observation had previously been thus misdiagnosed and had consequently been subjected to a vain search for a parathyroid tumor. The fact that the lesions are unilateral or mainly unilateral and that the unaffected bones are normal should be enough to exclude hyperparathyroidism. Furthermore, the serum calcium value is normal in practically all cases of polyostotic fibrous dysplasia. Occasionally however, it may be slightly above the upper limit of the normal. For instance, it was 11.0 mg. in one of our cases.

Treatment, Parathyroidectomy: In principle, the treatment consists of surgical removal of the offending parathyroid tissue. When this is successful, the pathologic state is abruptly arrested and soon begins to be reversed. In fact, substantial healing of the skeletal lesions may be manifest within a few months, even to the point of great reduction in the size of cysts and brown tumors. On the other hand, deformities do not become spontaneously corrected to any great extent after they have once developed.

Churchill and Cope[23] and Lahey and Haggart,[24] among others, have discussed the surgical problems involved, and also describe technical procedures facilitating accession to aberrantly located enlarged parathyroids. In at least four out of five cases of hyperparathyroidism, the offending parathyroid tissue consists of a single parathyroid adenoma. Occasionally, two adenomata are encountered at operation, in which case both should be removed. However, there are also cases (such as that of Hellström[25]) in which, after the removal of one adenoma, the impermanence of the resultant remission of the symptoms forces one to the conclusion that another adenoma must have been present which was missed. In addition, there are cases in which the possibility exists that the second adenoma only developed some years after the first one had been removed. Indeed, this seems to have been what happened in Mandl's

original case. After having maintained remarkable improvement for a number of years, the subject suffered a relapse, and this was logically attributed to the development of another adenoma. The irony of the situation is that, on re-exploration, Mandl[26] was unable to find a second adenoma, the latter probably being aberrantly located.

If, as is the case sometimes, the hyperparathyroidism is being caused by idiopathic parathyroid hyperplasia instead of adenoma formation, the surgical treatment presents particularly knotty problems. This is so because all four of the glands may be hyperplastic and there is danger of intractable tetany if all four are removed. On the other hand, if all four are not enlarged, there is no assurance that the remaining gland or glands will not subsequently undergo hyperplasia and thus induce recurrence of the symptoms. Albright and associates[27] recommend that three of the hyperplastic parathyroid glands be removed and the fourth partially extirpated so that at most no more than about 400 mg. of parathyroid tissue remains. In their experience, the effect of this procedure upon the state of hyperparathyroidism was to correct it permanently so far as present indications go. My experience with one case of this type, in which only two hyperplastic glands were removed, was that there was a rapid recurrence of all the manifestations of hyperparathyroidism within a few months. It has occurred to me that in such cases it might possibly also be advantageous to remove three of the parathyroid glands and all but a tiny fragment of the fourth and immediately transplant some of the parathyroid tissue into the abdominal wall. Here it would be easily available should removal of additional parathyroid tissue be indicated later on. In any event, in these cases, the surgeon must recognize the danger on the one hand of recurrence of the hyperparathyroidism from regrowth of the remaining stump and on the other of the development of intractable hypoparathyroidism from damage to the essential remaining tissue.

Postoperative Complications and Precautions: Hypoparathyroid tetany associated with the development of a hypocalcemia is a common postoperative complication. Often on the day following the operation, numbness and tingling—precursors of the tetany—already appear in the fingers and toes. Another postoperative complication which is common is oliguria. This usually corrects itself, however, after a few days. It may be noted that if, at the time of operation, advanced renal damage (nephrocalcinosis or pyelonephritis) exists, great danger of subsequent

death from uremia will remain.

Immediately after parathyroidectomy, precautions should be taken to prevent the onset of tetany. Large amounts of soluble calcium salts given by mouth are often effective. Because of the rapidity with which calcium salts are eliminated after ingestion, it is also desirable to give them frequently. For instance, 4 grams of calcium lactate may be given every 2 or 3 hours during the day and perhaps somewhat less often during the night. When the presence of tetany makes prompt effects urgent, the intravenous injection of 10 cc. of calcium lactate or gluconate may be necessary. If the administration of calcium by mouth does not adequately elevate the serum calcium, the desired result can be achieved through the supplementary injection of parathormone. To this end, 10 or 20 units of the parathyroid extract may be given several times daily for a while (subject to control by determinations of the serum calcium). In addition, the diet of patients suffering from latent tetany should be low in phosphorus. It may well be supplemented by large therapeutic doses of viosterol (60 to 90 drops, three times a day), or any of the more potent recently developed vitamin D preparations. This treatment should be cautiously continued for a number of weeks, by which time the serum calcium will probably have risen above the tetanic level. In intractable cases of hypoparathyroid tetany, homotransplantation of parathyroid tissue gives some promise of success.

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GENERAL CRYMOTHERAPY: A SYMPOSIUM*

FOREWORD

In July 1939, it was decided to make a clinical investigation of local and general crymotherapy at the Lenox Hill Hospital, New York. Accordingly a specially equipped, thermostatically controlled, air-conditioned room with a capacity of two beds was constructed. Intern and nursing personnel were thoroughly familiarized with clinical and technical details of general crymotherapy. On October 17, 1939, the first patient was subjected to the so-called artificial hibernation. This symposium is an account of four months' experience with this procedure.

Rationale and Description of Method. Selection of Cases. Conditions Treated

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THE originators of the so-called "Artificial Hibernation Treatment" (Crymotherapy) were Temple Fay and Lawrence Smith of Temple University Medical School, Philadelphia.

Fay, in the course of taking routine skin temperatures as part of standard neurological examinations, found that the skin over the breasts was constantly several degrees warmer than the skin above and below this region; furthermore, the skin of the extremities below the elbows and below the knees was regularly from 6° to 20° F. cooler than that of the rest of the body. This finding he correlated with the well-known fact that in generalized carcinomatous secondary involvement of the bony skeleton, the bones of the extremities below the elbows and below the knees were rarely, if ever, affected. Fay thought that cancer cells in the blood stream actually reached bones of the extremities, but failed to survive because it was too cool for them there.

* Given February 20, 1940, before the Section on Medicine of The New York Academy of Medicine.

With this idea in mind, namely, the possibly deterrent effect of cold on cancer, he decided to make a clinical trial in the case of a woman with a far advanced carcinoma of the cervix. For months she had been taking several grains of morphine daily, in spite of which, her pain was so severe that she had been referred to Fay for chordotomy. It was decided to defer operation to see what the local application of cold to the fungating mass in the vault of the vagina might accomplish. Accordingly there was improvised a round metal container through which water was constantly circulated at a temperature between 40° and 50° F. Within 36 hours, pain had gone, and as time went on, the ulcerating mass began to diminish in size and, by the end of 5 or 6 weeks, had completely healed. Biopsies taken before and during the treatment showed, according to Lawrence Smith, that under cold, the carcinoma cells disintegrated, whereas, the normal connective tissue and normal blood vessels survived. The woman was temporarily restored to normal activity for several months, then developed a secondary brain metastasis, from which she eventually succumbed. Following this first cast of local application of cold, the method was applied to ulcerating cancers of the breast, cheek and skin. In all of these there was improvement locally, with recession in size of tumor and even healing of the ulcer.

After about 2 years experience with this local cooling treatment, Fay had the courage to initiate cooling of the body as a whole for cancer located in regions not accessible to local cooling, for example, intractable pain from cancer involving the spine, pelvis, or abdomen. Here the patient was put to sleep by rectal administration of avertin. This method of cooling the unconscious or semi-conscious patient from ten to eighteen degrees below normal for periods from a few hours to as long as 5 days is the so-called "Artificial Hibernation," "Frozen Sleep," or as we call it here, "Crymotherapy."

The patient receives chloral and bromides the night before, luminal the next morning. A Levine or Einhorn tube is passed into the stomach, then avertin or evipal by rectum or intravenously renders the patient unconscious. He is now brought into an air-conditioned room, maintained at a temperature of 55° F.; is laid naked on a bed; the thermocouple is inserted into the rectum; a rubber-covered wire cable leads from the patient's rectum to the recording dial on the wall. Wrists and ankles are tethered with padded restraining loops. The patient's

trunk, from shoulders to half way down the thighs, is now packed in loose ice, the fragments of which are not larger than those of nut coal. The ice pack is maintained until the rectal temperature reaches 90° F. This usually takes from 1½ to 2½ hours; in one very obese patient as long as 20 hours. When 90° or 91° by rectum has been reached, the ice is removed, the patient dried, and at a room temperature of 55° F., the patient's rectal temperature goes down to the 80's.

Should the temperature become too low, blankets and lukewarm hot water bags surround the patient. Should the temperature begin to rise, ice bags without cloth coverings are applied to the trunk and upper thighs. Temperature, pulse, respiration and blood pressure are charted every half hour. A telephone in the room enables the nurse to call resident physicians at any time should the patient's general condition, color, respiration, or pulse show any marked changes.

Through the stomach tube, 2 ounces of normal saline with 10 per cent glucose are instilled every hour. For restlessness, sodium amytal or sodium luminal or even seconal are given in suitable quantities. The 20 per cent paraldehyde in gum acacia, orginally used, was abandoned as too irritating to the gastrointestinal tract. Twice a day the stomach is siphoned empty, and once a day the stomach is lavaged with a quart of normal saline, one pint at a time.

When it is time for discontinuing treatment, the air-conditioning apparatus is shut off and the room is allowed to come up to normal room temperature. The patient is covered with blankets and the body temperature slowly rises to normal. This usually takes 6 to 8 hours. The patient is not returned to the ward until normal temperature is reached. Experience has shown that nurses must be warmly dressed to care for these patients in a room at 55° F. The nurse is on for a period of 4 hours, then is relieved by another, and returns again after 4 hours to complete the second half of her 8 hour tour.

Selection of cases and conduct of this clinical investigation were assigned to a committee on which were representatives of surgery, general medicine, gynecology, pathology and physical therapy. Only cases of microscopically proven malignancy, inoperable and radioresistant were considered (140 applications; 26 acceptances).

Patients considered suitable for acceptance were those still up and about or in fair general condition; if bedridden (carcinoma of bladder, for example), with intractable pain or large, measurable tumor masses.

Grounds for Rejection*

1) Bed ridden patients, as a rule are too weak and with too brief an expectancy of life.
2) Patients with marked anemia (Hb. 60 per cent or less), as likely to develop necrosis of uvula, or of mucous membrane of cheeks.
3) Patients with carcinoma of stomach, as unlikely to absorb fluids and sedatives effectively.
4) Patients with lung metastases. Their presence, demonstrated by x-ray, increased the hazard of pneumonia. A few scattered metastases did not indicate rejection, but lungs riddled with metastases or a chest full of fluid precluded acceptance.
5) Patients with pathological fracture of the femur. The markedly reduced peripheral circulation while under general crymotherapy made the use of fixation by splints or casts hazardous. The unconscious patient's position must be changed from time to time to avoid the possibility of decubitus.

Conditions treated to date:

Carcinoma	22	Melanoma	1
Sarcoma (neurogenic)	1	Leukemia (acute)	2
Drug addiction	1		

Locations of Carcinoma (primary):

Prostate	2	Rectum	2
Breast	6	Thyroid	1
Colon	2	Urinary bladder	3
Uterus	3	Liver	1
Ovary	2		

In addition to malignancies it was appreciated that the effects of cooling might be tried out in many other fields, for example:

1) Intractable pain from other causes than carcinoma or sarcoma.
2) Tropical blood parasitic diseases resistant to commoner forms of therapy.
3) Drug addictions.

Incidental to relief of intractable pain from carcinoma it was found the patients had lost their craving for narcotics. Consequently,

* Formulated during this series and in part based on experience gained in observation of first patients.

the method was tried by Fay and Smith on addicts with no cancer, with several apparently successful deprivation cures. At least the period of deprivation was passed by the unconscious patients who afterwards, for the time being, seemed to live without the drug without suffering discomfort.*

4) Mental diseases, such as schizophrenia.

Conclusions Regarding General Crymotherapy

1) It was possible to reduce patients' temperatures from 10° to 18° F. below normal for from a few hours to 3 days. (Counting from time 90° F. was reached on way down to time 90° F. was reached on way out. Totalling 2,856 hours below 90° in 65 inductions on 26 patients.)

2) Inductions can be repeated, at intervals, as many as five times or more depending on the patient's general condition.

3) Risks from pneumonia and from nephritis seemed not as great as might be expected.

4) In malignancies, striking relief from intractable pain with discontinuance of narcotics was noted in eleven of seventeen patients.

5) Sooner or later pain returned, sometimes less severe, in others just as severe as before treatment.

6) As time went on progressive cachexia was noted.

7) Perhaps, if intervals between treatments were made shorter, a difference in recurrence of pain and progress of cachexia might be noted. This is to be given a trial; we have not had enough experience.

8) Our material, available during the past four months, has not afforded sufficient experience regarding the effect of local refrigeration to justify drawing conclusions.

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* Details of the one case observed by us may be reported here: A woman of 46 had, for at least 15 years, been taking 6 to 8 grains of morphine daily. She was subjected to 4 days' crymotherapy at 92° F.; then for 1 day more at 98.6° F., still under sedatives; 5 days in all, during which she stood the treatment well. Afterwards, for 2 days she was never left alone one moment. Since then for 8 weeks she has had no craving, and, for the first time in 7 years, menstruated normally a few days ago. It was interesting to note that, while under crymotherapy, gastric hypersecretion began at the end of the first 24 hours, amounting to between 1500-2500 cc. in 24 hours and requiring intravenous replacement of fluids by 5 per cent glucose in normal saline. The gastric hypersecretion gradually subsided by the fifth day, when she was able to absorb fluids normally once more.

Cardiovascular Aspects

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The changes in the circulation caused by cooling the body are approximately what one would expect. After a preliminary rise, the rate of the pulse is decreased, but not in proportion to the temperature. It is unusual, even with the rectal temperature below 85° F., to observe a rate of less than 50 beats per minute. Irregularities are most often due to sinus arhythmia or auricular fibrillation.

The blood pressure varies considerably. With short exposure of the patient to cold, it may show no significant change. During the "induction period" the systolic pressure, the diastolic pressure, or both may rise, or a typical epinephrin effect may be obtained, the diastolic pressure rising and the systolic falling. Quite consistently both show considerable decrease after long exposures. Often the blood pressure cannot be ascertained by the auscultatory method. Both arterial constriction and decreased arterial flow probably contribute in some measure to the difficulty of hearing Korotkoff's sounds.

The peripheral vascular tree undergoes profound constriction. Large arteries of the caliber of the dorsalis pedis, posterior tibial, or radial may be impalpable at low temperatures. Veins are often so constricted as to make simple venipuncture exceedingly difficult. A decreased body temperature is said to induce Raynaud's phenomenon even in normal individuals.[1] If Lewis and Pickering's[2] definition of Raynaud's phenomenon be accepted, namely, that the involved parts "become fully cyanotic or waxy," it may then be stated that no example of digital artery spasm was observed either in the hands or feet of the patients.

Observations elsewhere[3] have shown that the circulation time in the peripheral vessels is prolonged when the temperature of the body is decreased. With the slowed pulse, low arterial pressure especially in the later stages, the obvious generalized vasoconstriction, and the slowed circulation time, it is plausible to assume that the cardiac output per minute is decreased. However, direct measurements of this variable are still to be made.

Electrocardiograms are interesting, but difficult to obtain because

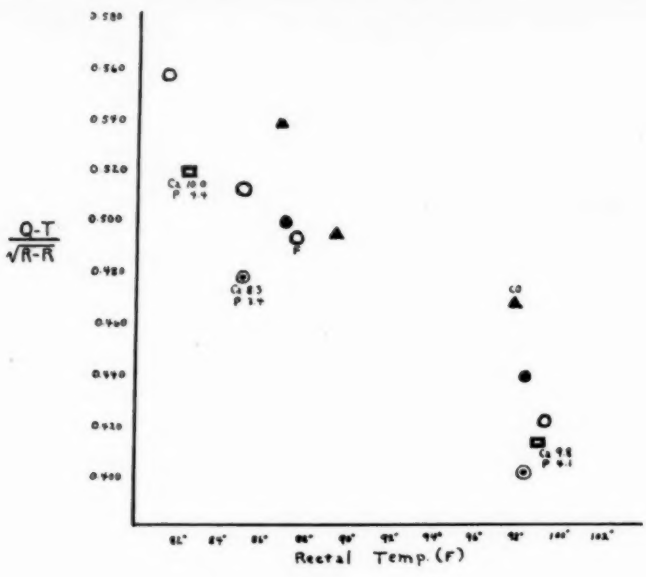

Chart 1

Chart 1—Twelve observations in 5 subjects (indicated by different symbols) on the relation of rectal temperature in Fahrenheit to the length of electrical systole expressed as Bazett's index (K = electrical systole $/\sqrt{\text{cycle}}$). Ca, serum calcium; P, serum phosphorus; CO, a patient with myocardial infarction 18 months before; F, auricular fibrillation. Two of the five patients were women. Their control values are within the normal range of K. The three men showed control values somewhat above the maximum normal, explainable in one on the basis of myocardial infarction.

of shivering. Wherever possible precordial Leads V_1, V_3, and V_5[4,5] were recorded with an oscillograph type of instrument at half-normal sensitivity, in addition to the standard leads. In nine subjects the most constant change in the electrocardiogram was an alteration in the form of the final ventricular deflections, and a prolongation of electrical systole. The accompanying Chart I, which includes twelve observations on five subjects, reveals almost a linear, though inverse, relationship between temperature of the body and the length of electrical systole expressed as Bazett's index.[6] However, when the patient is warmed again, the Q-T interval does not return to normal for many hours and may not do so for several days (Fig. 1). Even when it does reach its control value, some abnormality of the T-wave, always present during crymotherapy, may persist for some time. Lengthening of elec-

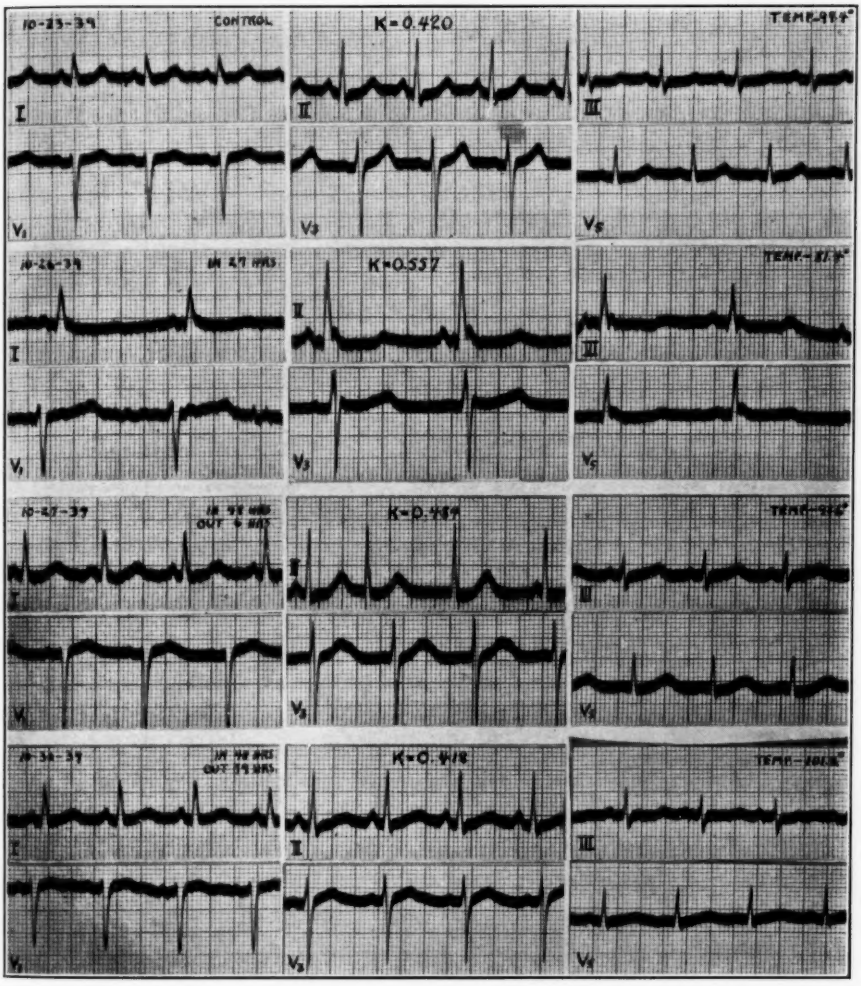

Figure 1

Figure 1—Standard electrocardiograms (I, II, III) at normal sensitivity of the string and precordial potentials (V_1, V_3, V_5) at half-normal of case, D. U., age 39, carcinoma of the transverse colon with generalized metastases. The date of the recording, the rectal temperature at the time, and the systolic index, K, are recorded on each curve. "In 27 hours" means the time the patient's temperature was below 98° F. "Out 6 hours" means the time after the patient's temperature had returned to levels above 98° F.

trical systole was not accompanied by any significant change in the serum concentration of calcium or phosphorus.[7,8] These facts suggest that the process responsible for prolonged electrical systole is a pathological one rather than a simple chemical retardation due to cold. Of interest was one patient who showed no prolongation of the Q-T interval during the therapy. She was receiving digitalis at the time, a drug known to shorten electrical systole[9].

In four instances an unusual T-wave was encountered, usually recorded best in Lead II (Fig. 1, 10/26/39), but also seen in other leads. It was observed only when the temperature of the subject was below 84° F. This T-wave was characterized by a summit immediately after QRS, a return to the baseline, and a final summit smaller than the first. The precise significance of this unusual deflection is not known, but it is surmised that it may be the first evidence obtained in man in support of the dipolar nature of the regression process in cardiac muscle.[10]

The initial ventricular deflections did not reveal the same sensitivity to cold as the final ventricular deflections. However, there was sufficient effect (Fig. 1) on electrical excitation to cause slight widening of the QRS interval, and distinctive changes in the separate deflections. Similar remarks apply to the auricular wave.

Auricular fibrillation was observed in four of the nine subjects. This abnormal rhythm was encountered only when the temperature was above 85° F. In one subject it was abolished by a lower temperature.

No premature systoles were recorded while the subjects were abnormally cold. Soon after removal from the crymotherapy room, one subject showed a His-bundle premature systole followed by a temporary shift of the pacemaker to the His-bundle (Fig. 1, 10/27/39, Lead II).

Summary

Decreased temperature of the body was observed to have the following effects on the circulation: the pulse rate is slowed; the blood pressure is variable but usually falls if an abnormally low temperature is maintained for more than 24 hours; there is marked generalized arterial, arteriolar, and venous constriction; abnormalities of the T-wave in the electrocardiogram are always present, and of the QRS group occasionally present; auricular fibrillation is common; electrical systole is prolonged, principally due to a delay of the recovery process, not related to changes in serum calcium.

Hematology

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One control, a morphine addict, was treated for five days under crymotherapy. After the first day the hemoglobin and red blood count increased slightly. The total white count went up appreciably, with a rise in the percentage of polymorphonuclears, and a shift to the left. The sedimentation rate and platelets decreased. The cell volume went up. Toward the end of the treatment, the hemoglobin and red count dropped. The white count remained the same. There was a gradual return to a normal blood picture with discontinuance of the treatment.

In the carcinoma patients, a short treatment was associated with a rise of the hemoglobin and the red count. There was a marked increase of the white count and percentage of polymorphonuclears, with more immatures. The sedimentation rate and platelets decreased, and the cell volume increased. As for bone marrow from sternal puncture, the total nucleated cell count dropped. The percentage of granular elements increased, while the erythroid elements decreased. During the longer periods of treatment, the findings remained the same, except for a drop in the hemoglobin, red count and cell volume.

Two patients with leukemia were treated—one lymphatic and the other myeloblastic.

The lymphatic was in the last stages of the disease, and aleukemic. He showed no changes during treatment. The bone marrow was completely replaced by lymphoblasts, both by sternal puncture and at autopsy.

The acute myeloblastic patient was given two treatments of 12 hours each. The total white count dropped from 50,000 to about 10,000 during each treatment, and stayed down for a few days thereafter. The differential count of 95 per cent myeloblasts did not change, and the marrow was completely replaced by myeloblasts, during life and at autopsy.

Blood Chemistry

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In view of the small number of patients observed under crymotherapy and the absence of normal controls, no attempt is made to draw definite conclusions.

This report presents the results of observations in eleven patients from whom blood was obtainable before, and 24, 48 and 64 hours under crymotherapy. The non-protein nitrogenous constituents of the blood, the plasma chlorides, the cholesterol partition, calcium and phosphorus, red cell volume, and sedimentation rate were studied in this group.

The non-protein nitrogenous constituents, before treatment was started, were within normal limits, with the exception of one patient in whom the urea nitrogen was elevated, the value being 27.7 mg. This patient showed an increased urea content of the blood after 24 hours under crymotherapy, the figure at this time being 38.5 mg. One other patient also showed a rise in blood urea from 8.8 to 17.8 mg. None of the other patients in this group revealed significant changes in any of the non-protein nitrogenous constituents.

The plasma chlorides were within normal limits before and during crymotherapy. The plasma protein changes were also without significance.

Changes in the serum calcium and phosphorus were not significant, while the serum cholesterol partition showed the percentage of free cholesterol to be rather constant before and during crymotherapy.

The red cell volume was increased under crymotherapy in four instances, the increase varying between 14 and 20 per cent.

The initial sedimentation rate was increased in all of the eleven patients under observation. Under crymotherapy there was a definite fall in the sedimentation rate, with the exception of three patients, in whom there was no change. However, it was noted that within 48 hours after crymotherapy, the sedimentation rate in those thus observed returned to about the pretreatment level.

Basal Metabolism Determinations

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It has been shown by Rubner, Lusk and others that after short exposures to cold there is an increase in the basal metabolism rate as high as 180 per cent over the normal. This is ascribed to the mechanical and chemical mechanisms of heat regulation.

The effect of sedation and sleep have also been studied and it has been shown that the B.M.R. may drop 15 per cent during sleep. Ordinary sedatives, in therapeutic doses, have little or no effect on metabolism. Patients undergoing crymotherapy present an opportunity of studying the effect of prolonged low body temperature on basal metabolism, possibly for the first time.

Procedure: One or two days after admission to the hospital, a B.M.R. determination was made under the usual conditions, i.e., after a night's rest and in the fasting state. Several control tests were made after administration of glucose and saline by mouth and after small doses of sedative, such as are now routine in crymotherapy. These controls showed no remarkable deviation from the normal. The next determinations were made at the end of 24 hours of body temperature below 86° F., 48 hours, and in one case, 72 hours. Several patients were rechecked 24 hours after their return to the wards.

The results here presented were obtained on patients who were fairly quiet and coöperative. They were told that a breathing test was about to be done, and were asked to breathe slowly and quietly, which they did surprisingly well. There was, in some patients, moderate muscular twitching, but if this was at all marked, or restlessness increased, the test was discontinued. One nurse held the lips in place over the mouthpiece, another held the nosepiece in place, while we watched continuously for leakage and other factors which might give an erroneous result. Some patients could be tested at the end of 24 hours but were too restless at the end of 48 hours. The body temperature ranged from 85.5° to 86.2° F. There was a rise in two cases of from ½ to 1° F. during the test.

Results: Thirteen patients were tested. The highest B.M.R. prelim-

inary to crymotherapy was +39 per cent; the lowest, −12 per cent, Ten tests were run at the end of 24 hours. Of these, three showed an increase of 3 per cent over the preliminary B.M.R., and seven showed a drop of 2, 2, 10, 13, 17, 18 and 25 respectively.

Six tests were run at the end of 48 hours, one showing a rise of 14 per cent, and five showing a decrease of 10, 10, 17, 32 and 50 over the preliminary B.M.R.

One test run at the end of 72 hours showed a drop of 22 per cent. One patient, a drug addict, undergoing withdrawal treatment, was tested at the end of 24 hours. The B.M.R. was +17 per cent. Three patients tested after return to the wards, showed a B.M.R. about the same as the preliminary.

Tentative Conclusion: It would seem, from this small series, that in patients undergoing crymotherapy, there is a definite drop in the B.M.R. at the end of 24 hours and a further drop at the end of 48 and 72 hour periods. Since short exposures to cold have been shown to increase the B.M.R. noticeably, it may be concluded that metabolism is depressed by continued low body temperature.

Neurological Observations

THOMAS K. DAVIS

Neurologist, Lenox Hill Hospital

For various reasons my report is not based upon all the patients who have received crymotherapy. On eight patients I have done complete neurological examinations before and after the treatment and during the treatment have carried out as much of a neurological examination as is possible on a semicomatose patient.

In no instance were there any neurological findings after the treatment differing from the neurological status before. However, during the treatment there was in all cases a disappearance of the pupillary light reflex. In those patients in whom I have been able to observe the fundi, the fundi were normal, as one would expect.

In two instances, during the treatment, while the various deep reflexes were slightly if at all stronger than before, there were crossed tibial reflexes not previously observed. (These were absent following

the treatment.) Also in one patient in the treatment, a nil response to plantar stimulation was obtained. Both before and following treatment, this patient's plantar reflexes were normal.

This transient change of plantar response in one patient and the transient crossed reflexes in two other patients suggest that when the body temperature is reduced there is a tendency for the pyramidal tracts to lose part of their normal control. One finds that the coldness of the extremities tends to produce a pseudospasticity which is probably local. This being so, it is not easy to be dogmatic regarding the reflexes; but as I said before, the occasional appearance of crossed reflexes would seem to lie outside the province of the local status and may concern the temporary functioning of pyramidal tracts.

In one patient a hyperesthesia of the left side of the face, possibly occasioned by a metastasis, which was present before the treatment, was unchanged after the treatment.

On the mental side, during the treatment the patients were at times restless and uneasy. Although only semiconscious, they did in some instances resent the wrist restraints or ask to be covered. It was possible to get slightly in touch with the patient. One gave the name of the President when asked and added "9 and 7" correctly; but the same patient did not respond when asked to give the name of the hospital. After the treatment this patient had no memory of anything which had happened. Another patient, though semicomatose, opened her eyes on command. She seemed to understand a question regarding how she felt and replied "good"; afterward she had no memory for any part of the period.

Another patient even remarked—"Am I being a good guinea-pig?" Also she asked if treatment was being given her for a longer period that time. But this patient did not recall these things afterward.

Another patient appeared to understand simple questions but mumbled the same perseverated replies to all questions. Also she had complete amnesia for this afterward.

I am not inclined to speculate on the factors involved in this kind of transient accessibility. Its transient character reminds one of the semicoma seen in epidemic encephalitis. One wonders whether the reduced temperature is the factor which works to produce the complete amnesia afterward. I doubt if the sedation employed alone explains the amnesia.

In retrospect, none of the patients have looked upon the treatment as unpleasant.

Temperature Observations

MADGE C. L. MCGUINNESS

Director of Physical Therapy, Lenox Hill Hospital

The usual skin temperatures observed in this study are entirely relative, since we have not the required constant-temperature room for this purpose, and in the crymotherapy room our semi-conscious patients cannot coöperate as well as the usual subject studied.

Observations on two men and one woman are shown: Joseph M. (M.1), Age 41, with cancer of the rectum, the most nervous of the twenty-seven patients, is alternately apprehensive and euphoric (Chart 2).

James M. (M.11), Age 47, with lower gastrointestinal carcinoma, less nervous than M.1 ordinarily, but extremely restless and spastic in the crymotherapy room (Chart 3).

Mrs. C. (F.5), Age 37, with cancer of the left ovary, most coöperative and docile of all the patients, who was in a state of tonus apparently both in and out of the crymotherapy room as evidenced by her reduced oscillometric readings (Chart 4).

In the crymotherapy room, constant sedation and hourly feedings of glucose in saline had a distinct bearing on the temperatures. Most important was the almost constant shivering and, despite restraining cuffs and anklets, the tendency to move continuously.

In the crymotherapy room the temperature varied, being 55°F. at the wall where the recording thermometer wrote its story, 60°F. at the opposite wall near the window, 59°F. at 12 inches from the knee, from 64° to 66°F. on the bed between the calves and, on the Dakin pad covering the crotch, 71°F., rising or falling as the rectal temperature varied.

The units used were the U.M.A. and the Leeds-Northrop recording temperature thermocouple specially made for this work. As Dubois[1] and Hardy[2] contend, each piece of work is unique as it involves so many variables, beginning with the air temperature of room or thermocouple and ending with the personal equation; running the gamut in between, of patient and worker coöperation, liquid intake, changes in rectal and room temperature, exercise, shivering and general condition of patient.

Chart 2—COMPARISON OF SKIN TEMPERATURES

Mr. M. 1. Age 41 | Ca. Rectum (Intestinal Fistula)

		° F.		*Crymotherapy* ° F.	
Room Temperature		78.	55.	Head Wall	60. Foot Wall
Thermocouple		74.5	60.		
Between Calves		78-80	59.-60.		
Rectal			87.75		
Mouth		99.2			
B.M.R. —12	Wgt. 136		Wgt.—122		
B.P. 130			B.P. 118 — 100		
90			80	70	
Great Toe	R.	84.	60.25		
	L.	85.	62.25		
Ball	R.	85.	62.50		
	L.	85.	63.75		
Heel	R.	84.	63.25		
	L.	86.5	62.75		
Ankle	R.	87.5	63.75		
	L.	85.75	69.25		
Calf	R.	87.75	66.25		
	L.	85.75	67.50		
Knee	R.	88.	68.		
	L.	86.25	73.		
Thigh	R.	89.75	78.		
	L.	89.25	81.5	Urine 82. (?) Rectal 87.4	

Oscillometric Readings

	Ankle	*Calf*	*Thigh*	*Ankle*	*Calf*	*Thigh*	
Right	3.00	4.25	2.50	faint	0.25	0.50	spastic
Left	2.50	3.25	2.25	faint	0.25	0.30	shivering

Chart 3—COMPARISON OF SKIN TEMPERATURES

Mr. M. 11. Age 47 | Ca. Lower Intestine Wgt. 138 (was 185)

		° F.	*Crymotherapy* ° F.	
Room Temp.		71.	55. Head Wall	60. Foot Wall
Thermocouple		72.	60.	
Rectal		98.2	88.	
Between Calves		74.	64.	
B.M.R. —13				
B.P. 116 — 102			B.P. 130 — 90 lowest	
90 78			88 50	
Great toe	R.	79.	67.	
	L.	77.75	63.25	
Ball	R.	80.75	66.	
	L.	79.25	64.	
Heel	R.	82.25	66.	
	L.	80.	64.25	
Ankle	R.	83.25	67.	
	L.	81.75	66.	
Calf	R.	85.	72.	
	L.	85.	73.	
Knee	R.	90.25	71.75	
	L.	89.50	74.25	
Thigh	R.	91.5	75.75	
	L.	89.75	79. = Chill 78. quieter	
Breast	R.	89. to 90.75	72. to 73.75	
	L.	89.75 to 90.50	71. to 72.	
			Urine 84. Rectal T. 86.9	

Oscillometric Readings

	Ankle	*Calf*	*Thigh*	
Right	1.75	2.75	3.50	Unable to take readings—Constant
Left	1.25	2.00	3.50	shivering, spasticity, continuous movement.

Chart 4—COMPARISON OF SKIN TEMPERATURES

Mrs. C. Age 37 | Ca. Left Ovary Wgt. 103

		° F.	*Crymotherapy* ° F.	
Room Temperature		71.	54. Head Wall	60. Foot Wall
Thermocouple		70.	60.	
Between calves		76.5	59.	
Rectal 10 minutes		100.4	86.	
Vaginal 10 minutes		100.8		
B.M.R. + 14				
Great toe	R.	70.5	61.5	Spastic.
	L.	73.	62.25	Left arm markedly
Ball	R.	75.25	64.	adducted.
	L.	75.25	64.25	Marked tonus.
Heel	R.	77.25	64.	
	L.	75.25	64.25	
Ankle	R.	82.	65.	
	L.	81.5	66.75	
Calf	R.	84.75	69.	
	L.	86.75	69.	
Knee	R.	87.	67.25	
	L.	87.25	Ice applied	
Thigh	R.	87.25	Rectal T. rose	
	L.	87.75	from 86 to 87.45	

Oscillometric Readings

	Ankle	*Calf*	*Thigh*	*Ankle*	*Calf*	*Thigh*
Right	0.5	1.50	1.75	0.25	0.5	1.00
Left	0.5	1.25	1.75	faint	0.5	1.00

When the patient was especially active, moving the right arm and hand continuously, trying to take off the ice bags or attempting to cover himself, the temperature varied on either side, from tenths to 3 or more degrees Fahrenheit. This is shown in the chart of M.11 who was never still for one moment and shivered continuously. Drugs seemed to have very little effect upon this patient.

Oscillometric readings were taken in the crymotherapy room when possible and showed marked variations and decreases in oscillations, with shallow and deep breathing, chills, exercise and spasticity.

The range of error was constant for the devices used. Between 90° and 110°F., the degree of error was plus or minus 1. When the temperature was below 90°F., the degree of error was plus or minus 1.25. This range has been established by the U. S. Bureau of Standards.

Conclusions: Different parts of the body cool to varying degrees. Shivering and movement increase temperature.

Greater changes occur from a higher temperature of 78°F. than from 71°. Vasoconstriction is marked, thus decreasing the conductivity of skin, so that the blood is held within the body. Further studies are required to properly evaluate varied findings in temperatures at other levels than these shown.

Urologic Aspects

HERBERT R. KENYON

Urologist, Lenox Hill Hospital

There were eight patients with involvement of the urogenital tract, falling into three groups:

1. Primary neoplasms.
2. Secondary invasion of the urinary tract.
3. Extra-urinary tumors producing obstruction.

Group 1 includes two cases of prostatic carcinoma and three primary vesical neoplasms. The first patient with carcinoma of the prostate also had widespread skeletal metastases with pathologic fracture of a rib. His response to radiotherapy was poor and his pain uninfluenced by large doses of opiates. Although his condition was precarious, he re-

ceived one treatment at the urging of his physician which was followed by partial subsidence of pain. Unfortunately, he developed pneumonia on the third day after treatment and died four days afterward. The second patient has shown a more satisfactory response than any of the others. He was known to have a carcinoma of the prostate for nine months, during which time his condition had steadily deteriorated, the outstanding complaint being severe backache due to sacral metastases. This was resistant to x-ray therapy and alcohol injection of the sacral nerves. He had also developed a vesical calculus and lost 50 pounds within 6 months. It was impossible for him to lie on his back for more than a few minutes at a time. Transurethral resection and lithalopaxy were performed, the tissue showing adenocarcinoma. After the first session in crymotherapy it was possible for him to lie comfortably on his back without the large doses of morphine and cobra venom that had previously been necessary. Although subsequent biopsies have shown no change in the structure of the tumor, and x-rays indicate further spread of the metastases, rectal palpation reveals a recession in the size and consistency of the primary tumor. Lately there has been a partial recurrence of pain, in a different location, for which additional treatment is now being administered.

Two of the patients with primary vesical neoplasm showed little benefit from treatment except for transitory diminution in the degree of pain. In both there were extensive recurrences following partial cystectomy and radiation therapy. One was complicated by a vesico-vaginal fistula with bony metastases, while the other presented extensive involvement of the inguinal and iliac nodes with edema of the legs. Both died within 3 months after receiving treatment without evidence that they had been favorably affected. The third patient had symptoms for 8 months and a papillary carcinoma had been observed 3 months before admission. It had resisted radiation and our admission cystoscopy disclosed a growth involving almost the entire right half of the bladder, including the sphincter and ureteral orifice, without demonstrable metastases. Following the first session of crymotherapy, sufficient relief was obtained to permit a considerable reduction in the dosage of narcotics. Further treatment resulted in definite betterment of both the symptoms and the general condition of the patient, despite the fact that later observations reveal no change in either the gross or histologic characteristics of the tumor.

Group 2 includes two cases of cervical carcinoma with invasion of the bladder wall. The first patient also had extension to the rectum, peritoneum and omentum. Treatment resulted in a fleeting diminution in the severity of pain, but she died soon afterward of uremia. The second patient also showed evidence of ureteral compression and inadequate renal function. Symptomatic improvement in the patient was definite and sustained, despite the complete lack of any observable improvement in the objective findings, until death from uremia supervened 3 months later.

Group 3 is represented by a single patient, who also had a carcinoma of the cervix with ureteral compression without actual involvement of the bladder. Her symptoms were unaffected by crymotherapy, but some relief followed attempts at ureteral dilatation. She was permitted to go home for the holidays and, while there, was subjected to an emergency operation, the nature of which is not known, from which she failed to recover.

Some measure of subjective improvement was noted in the majority of these patients. In a few it was insignificant and ephemeral, while in two it has been more definite and prolonged. Estimated in terms of the analgesic and narcotic drugs required, the results have been appreciable in several cases. There were no instances of disappearance of either the primary tumor or of metastases, although in one case a demonstrable recession in the extent and firmness of a prostatic cancer was observed.

The Pulmonary Complications

JOHN F. DIXON

House-Physician, Lenox Hill Hospital

Of the twenty-six patients treated by January 20, with 53 periods of crymotherapy, six patients developed pulmonary complications. There were five bronchopneumonias. The sixth, apparently a bronchopneumonia, was a case of far advanced acute lymphatic leukemia proven at autopsy to have diffuse leukemic infarction of the lungs.

The first pneumonia case was a man of 63, with carcinoma of the prostate who was far gone when first seen. He was profoundly anemic,

with bones moth-eaten in x-rays, and with pathological fractures of several ribs. Following 38 hours of crymotherapy, respiration rose to 50, the temperature went to 104° and signs of bronchopneumonia were heard. Type 20 pneumococci were recovered in the sputum. X-rays at this time showed a possibly small amount of scattered infiltration at both bases. There was no leukocytosis, white blood counts remaining below 11,000. The patient died at the end of 7 days. His death was felt to be due to far advanced carcinomatosis, with a slight terminal bronchopneumonia.

The second case, that of a 31 year old woman in the last stages of acute myeloid leukemia, developed a cerebral thrombosis and infarction following her second period of treatment. Lobular pneumonia, along with small abscesses and leukemic infiltration, were incidental findings at autopsy.

The third case, a woman of 50 with advanced metastatic carcinoma of the breast, had pulmonary metastases, revealed by x-ray, before treatment. Signs of bronchopneumonia developed during the second period of crymotherapy. X-rays at this time showed an increase in the size of the pulmonary metastases, with only slight pneumonic infiltration. Sulfapyridine was given and the pneumonia subsided. The patient expired a month later of cachexia. Autopsy showed metastases in every organ of the body, including the spleen. There was no pneumonia present at death.

The fourth case, a woman of 53, with carcinoma of the bladder, aspirated some vomitus and mucus during her second treatment, and developed an extensive bronchopneumonia, proven by x-rays. Sputum examination revealed type 19 pneumococci. She recovered in 5 days, to die a month and a half later of uremia.

The fifth and last case, was that of a 46 year old man who had a carcinoma of the bladder with extensive local and general metastases. He also had a history of coronary thrombosis. This patient developed fever and signs of consolidation following his third treatment. X-rays showed a combination of atelectasis, consolidation and infiltration, along with some pleural exudate. The acute symptoms subsided with treatment, but the patient expired 5 weeks later of diffuse carcinomatosis.

In short, of the twenty-six patients treated, eight had demonstrable pulmonary metastases. Four of these developed some degree of clinical bronchopneumonia. However, x-ray findings were slight and indefinite

in all of them. Of the eighteen patients whose lungs were clear, only one developed pneumonia, which was a result of aspiration.

Nose and throat cultures, routinely taken in all patients before treatment, were all negative for pneumococci and hemolytic streptococci. Pneumococci were recovered and typed from the sputa of two of the pneumonias, while in the other three, no causative organism could be found.

Although obviously this series is small, one gains the impression that the presence of pulmonary metastases may predispose to a complicating pneumonitis. On the other hand there were eighteen patients whose lungs were clear clinically and by x-ray, who had a total of thirty-five periods of crymotherapy, with only one pneumonia.

Roentgenological Observations

FRANK HUBER

Associate Radiologist, Lenox Hill Hospital

X-rays of bone metastases (in two patients) taken at suitable intervals showed definite increase in size of previously noted defects, as time went on.

Biopsies and Deaths

RUDOLF M. PALTAUF

Pathologist, Lenox Hill Hospital

Of the twenty-two cases of carcinoma receiving general crymotherapy, only eight were followed up with subsequent histological examinations. In five cases we were able to obtain from one to three biopsies during treatment and three of these were subsequently studied at autopsy. In two cases, the study was limited to a comparison of material obtained before treatment and the postmortem examination. One patient with malignant melanoma gave us the opportunity for histological study after one and after two treatments with crymotherapy.

In all of these biopsy studies, the histological picture of the tumor, its cell characteristics and the appearance of the surrounding tissue appeared identical in every respect with that seen in examinations before the treatment.

Of the five cases representing our autopsy material, three cases were carcinoma of the breast, one carcinoma of the uterus and one carcinoma of the colon. In the carcinoma of the breast, the metastases were most widespread, including in one case the spleen. The three cases of carcinoma of the breast showed acute inflammatory lesions in the pancreas which varied in degree from focal areas of necrosis to hemorrhagic pancreatitis with extensive fat necrosis all along the surface of the pancreas and adjoining mesenteric and omental fat. This apparently was the immediate cause of death in one patient. In two other cases of carcinoma of the breast, marked necrosis of the tumor tissue was noted in all the metastases and in the absence of evidence of a terminal pneumonia or other complications, the cause of death in these patients must be attributed to cachexia and some chemical changes due to absorption of the toxic products from the necrotic tumor tissue.

In the case of carcinoma of the colon, metastases were found in the liver and ovary. In addition, a moderate degree of coronary sclerosis was noted. This patient developed an intestinal obstruction and an emergency cecostomy was performed without apparent relief, shortly before death occurred.

The last patient in this series died of a massive pulmonary embolus, the origin of which could not be demonstrated, but apparently came from the veins of the lower extremities.

The two other patients who came to autopsy after treatment with crymotherapy had leukemia, one myelogenous and one lymphatic. They gave the usual findings in such cases and marked pulmonary edema and congestion with infarction in one and pneumonia in the other.

We did not find any regression of the primary tumors or metastases, nor were we able to demonstrate unusual cell alterations or any changes which could be interpreted as effects of crymotherapy on the neoplastic tissue. Nothing characteristic or uniform was found, except perhaps the acute inflammatory lesions of the pancreas which occurred in three of the five cases of carcinoma.

Local crymotherapy was followed up by histological examination in one case, a proven carcinoma of the fundus uteri. Five days after the

curettage, a cooling canule was inserted in the uterus. Through this canule, which represented a long loop of tubing, water circulated. It entered at a temperature of 34° and returned at 50°, with an estimated temperature of 40-45° in the uterus. This patient was treated for 10 days with this local cold application and subsequently the uterus was extirpated. In comparing the histological appearance of the tumor in the curettement and in sections from the uterus, we found that while the tumor tissue in the curettement was well preserved and without much degeneration or necrosis, the tumor in the sections of the uterus showed a very marked, extensive and deep reaching necrosis. The uninvolved endocervix, although exposed to the same trauma of the cold-applicator, showed only slight erosion of the surface. Twenty-one days elapsed between the curettage and the hysterectomy. In reviewing slides from other cases of carcinoma of the uterus where similar or shorter periods elapsed between curettage and hysterectomy, we did not observe such changes. It cannot be definitely stated whether or not these changes were due to crymotherapy.

Clinical Manifestations

(General observations; pain relief; mortality; local crymotherapy)

PAUL KURT SAUER

Associate Surgeon, Lenox Hill Hospital

Immediately following the application of ice there is a brief temporary rise of 1° to 1.5° F. As the effect of the evipal begins to wear off shivering becomes manifest and is most marked between 97° and 95°, then as the temperature goes down it diminishes. Usually temperatures were kept between 80° and 85° F. In two cases 79.6° F. was reached for less than 2 hours.

Basal metabolic rates and electrocardiograms cannot be accurately taken when shivering is pronounced.

There is coma vigil—the eyes must be instilled with castor oil and kept covered with vaseline gauze to prevent drying and possible corneal ulceration.

On the second and third days patients are quieter and less sedation is required.

Catheterization is done every 12 hours.

Upon emerging, often there is fever of 100°–101.5° F. which may last for 1 or 2 days.

There is more or less haziness of the sensorium for 24 to 48 hours after emergence.

Pain is often complained of upon first regaining consciousness. It is often only during the second 24 hours that one may determine whether relief from pain has come to pass.

Twenty-seven patients have been submitted to general crymotherapy. Twenty-two of these had carcinoma; one, melanoma; one, neurogenic sarcoma; two, acute leukemia; and one, drug addiction.

Regarding relief from pain, the twenty-four cases of malignancy (22 carcinoma, 1 melanoma, and 1 neurogenic sarcoma) fall into three groups:

First, a group of five with little or no pain; second, a group of eight with little or no relief of pain; third, a group of eleven with marked relief of pain.

In five patients of the second group, relief occurred for very brief periods:

1. A patient with carcinoma of the bladder with extensions to the vagina and the rectum. Pain only at urination. This was relieved for about 48 hours after the first induction, but recurred, and was not alleviated by subsequent inductions.

2. A patient with carcinoma of the breast with metastases and a healed pathological fracture of the femur; there was relief for about 24 hours.

3. A patient with carcinoma of the uterus with pelvic metastases was not relieved of her original pain in the left leg but was found, subsequently, to have an obstructed ureter. The obstruction was relieved and her pain subsided.

4. A patient with a neurogenic pelvic sarcoma experienced about 75 per cent relief for a period of only 36 hours after the first induction, then pain returned with original severity, and was not affected by a subsequent 3-day induction.

5. A patient with carcinoma of the breast with wide spread metastases was relieved for 72 hours.

Three other patients in this group experienced no relief of pain.

In the third group, prior to induction, all of the patients had been taking varying quantities of sedatives. Many of them required the administration of morphine over a period of months, and at times as much as 4 grains per day. Following the induction these same patients required no sedation, and even those who had had large doses of morphine over a period of months were comfortable and apparently had no desire for morphine. This relief varied in quality and length of time.

Eventually recurrence of pain occurred in all cases. In some, as early as 24 hours after cessation of treatment, and in one case the relief lasted as long as 8 weeks. In some, the recurrent pain was not as severe as originally, consequently these patients required less sedatives; in others, the pain on recurrence was just as severe as before treatment.

Pain recurred at sites other than originally noted in 3 cases. In one, a sciatic pain replaced the original sacrolumbar pain, but even then the patient was able to sleep on his back, which he had not been able to do for a year previous to his first induction. Incidentally, this was our first case, and his one question two days after emerging was, "When can I have another treatment?" In another, pain in the left hip replaced a pain in the cervical spine. In the third, severe abdominal pain was abolished, but pain recurrence manifested itself in the chest.

As a rule, visible and palpable subcutaneous metastases did not diminish or soften after general crymotherapy. However, two exceptions are worthy of note.

One was a patient with carcinoma of the thyroid with a tracheotomy. One week after her first induction it was noted that a nodule of the right lobe of the thyroid about the size of a walnut had disappeared, the carcinomatous granulations surrounding the tracheotomy wound had disappeared and new epithelium was beginning to grow from the edges of the wound.

The other patient had a carcinoma of the transverse colon, previously resected, with metastases to the liver, which was palpable four fingers' breadth below the costal margin and was stony hard. After the second induction, the liver's size had regressed so that it was barely palpable and felt considerably softer. Eight weeks later, however, the liver had again regained its original size and hardness. This patient had relief from abdominal discomfort for at least 12 weeks; but pain recurred in his chest, which was filled with pleural metastases, and was not relieved.

His general condition precluded further inductions.

Metastatic nodules in a breast scar and on the back of one patient were noted to have increased in size despite three general inductions.

Out of 27 patients inducted, 13 have died subsequently. The causes of death and the length of time after their last induction are as follows:

1.	E.	Carcinoma of prostate Pneumonia	6 days
2.	S.	Carcinoma of bladder Pulmonary embolism	22 days
3.	H.	Carcinoma of breast Cachexia, pancreatitis	31 days
4.	R.	Carcinoma of cervix Cachexia	44 days
5.	K.	Carcinoma of thyroid Suicide	22 days
6.	B.	Carcinoma of breast Cachexia, pancreatitis, shock	In room at end of induction with rectal temperature 97.5°F.
7.	V.	Neurogenic sarcoma Postoperative (N. Y. Hosp.)	22 days
8.	G.	Carcinoma of bladder Cachexia	46 days
9.	O'C.	Carcinoma of colon Obstruction, postoperative	2 days
10.	A.	Leukemia	1 day
11.	T.	Leukemia Cerebral hemorrhage	8 days
12.	H.	Carcinoma of breast Pancreatitis	6 days
13.	K.	Carcinoma of bladder Uremia	31 days

In two cases of acute leukemia—one lymphatic and the other myeloblastic—the course of the disease was not affected. We have had no experience with chronic leukemias.

Local Crymotherapy

Local crymotherapy implies local cooling of accessible malignant tumors. This is accomplished by means of suitable coils of rubber or metal tubing, or hollow metal containers of special conformation, applied to the tumor's surface, through which ice water (40°-50°F.) is kept circulating for 23 out of every 24 hours.

Two patients received local crymotherapy. One had carcinoma of the fundus uteri which received local crymotherapy for ten days before subsequent hysterectomy. The histological findings are reported by Dr. Paltauf elsewhere in this report. The other had metastatic carcinoma of the cervical nodes following an excision for carcinoma of the lip some years previously. At the time of admission the left side of his neck was stiff and indurated. Motions of the head and of the left arm were so painful that even reading a newspaper occasioned extreme discomfort. Within 24 hours after the local application of ice water coils, he himself called attention to the softening of the neck tissues and was able to use his left arm without pain. A week later the induration of the left side of the neck had diminished so that discrete glands were palpable. After two weeks, the mass in the neck had diminished to a size about 2 by 2 inches. He left the hospital soon after this and died at home 2 weeks later from a carcinomatous obstruction of the sigmoid and peritonitis.

Conclusions

1. In eleven out of seventeen cases of intractable pain due to carcinoma, there was sufficient alleviation of pain to obviate the necessity for the administration of narcotics for variable periods of time.

2. No significant histological changes at autopsy in the appearance of carcinomata treated by *general* crymotherapy have been observed.

3. Our experience with *local* crymotherapy is too limited to warrant comment.

4. Investigation of this method should be continued, not necessarily limited to carcinoma. Investigation might be made as to its applicability in such other diseases as Hodgkin's disease, lymphogranuloma venereum, subacute bacterial endocarditis, drug addictions, blood dyscrasias, and tropical blood-parasitic diseases of an intractable nature.

Discussion

W. Laurence Whittemore

Physician, City Hospital

Aside from Doctors Fay and Smith's report in August 1939 there is no reference to crymotherapy in the Index Medicus, and one may say that in New York our general knowledge of this procedure is based on the work carried on so ably in Lenox Hill Hospital and reported on so fully in this report.

It is learned that local tissues may be cooled down to 40°-50° F. without harm, and general hibernation demonstrates the fact that man's temperature can be cooled down 10°-18° F. for a period of 3 days duration.

In Philadelphia one patient was subjected to this treatment for 8 days.

A. T. Rasmussen[1] reported that Mares and Hillich in 1889 reduced the temperature in an hysterical woman to 92.50 Fahr.

Beginning with Buffon in 1749 many of these early experimenters have pointed out that exposure to cold alone will not produce true hibernation, but often a torpid condition that is entirely and physiologically different from true hibernation.

Marshall Hall[2] in 1831 demonstrated this when he found that after destroying the brain and spinal marrow in a truly hibernating hedgehog, the heart continued to beat for 10 hours. Cushing and Goetsch[3] in 1915 successfully demonstrated the same experiments on animals.

Marshall Hall 100 years ago also drew attention to the fact that hibernating animals were easily disturbed by noises and touch. This has been repeated so often that one might be forgiven for suggesting that all unnecessary disturbances and noises be kept minimal in the crymotherapy room. Observations might be made whether or not in induction some patients leaned more towards cold torpor, and others towards true hibernation.

One may wonder if there is not a link between the successful demonstration of regression of cancer tissue at 40° to 50°F. and that of general hibernation at 79°F. Possibly with further study of general hibernation this latter figure may be considerably lowered.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

MARCH 7— *The New York Academy of Medicine.* Executive Session—a] Reading of the minutes. ¶ Papers of the evening — Clinical manifestations and management of disturbances in water metabolism—a] Medical considerations, Dana W. Atchley, Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University; b] Surgical considerations, Frederick A. Coller, Professor of Surgery, University of Michigan; Discussion, John P. Peters, New Haven, William F. MacFee. ¶Report on Election of Members.

MARCH 21—*The Harvey Society (in affiliation with The New York Academy of Medicine)* The Sixth Harvey Lecture, "Utilization of Selective Microbial Agents in the Study of Biological Problems," Renè J. Dubos, Associate Member, The Rockefeller Institute for Medical Research.

SECTION MEETINGS

MARCH 5—*Section of Dermatology and Syphilology.* Presentation of cases—a] Skin & Cancer Unit of Post-Graduate Medical School, Columbia University; b] Miscellaneous Cases. ¶ General Discussion. ¶ Executive session.

Section of Surgery—The Section of Surgery held no meeting on its regular date but instead met with the Section of Medicine on March 19.

MARCH 12—*Combined meeting Section of Neurology and Psychiatry and the New York Neurological Society.* Presentation of cases—a] Recovery in amyotrophic lateral sclerosis treated with tocopherol (vitamin E); presentation of two cases, I. S. Wechsler; b] Supratentorial hemangioma with hemorrhage; presentation of two cases, Ira Cohen. ¶ Discussion—Joseph E. J. King, Joseph Globus. ¶ Papers of the evening—a] Spinal epidural infections; surgical and pathological consideration, Jefferson Browder. ¶ Discussion—Harold R. Merwarth, Ira Cohen; b] Focal cerebral ischemia and reactive gliosis following experimental vascular spasm, Francis A. Echlin (by invitation). ¶ Discussion —Harold G. Wolff, Lewis Stevenson. ¶ Executive session.

MARCH 13—*Section of Historical and Cultural Medicine.* Reading of the minutes. ¶ Papers of the evening—a] Jean Nicholas Corvisart, Physician to the Emperor Napoleon, Paul E. Bechet; b] An American Precursor of Freud, A. A. Brill. ¶ Discussion—Clarence P. Oberndorf. ¶ General discussion. ¶ Executive session; Report of Nominating Committee.

MARCH 14—*Section of Pediatrics.* Reading of the minutes. ¶ Papers of the evening —a] Observations on jaundice in childhood and in the newborn, Samuel B. Weiner (by invitation), Miriam Reiner (by invitation). ¶ Discussion by Harry Sobotka, Bela Schick; b] The allergy concept of the hypertonic state, Miner C. Hill. ¶ Discussion by Sidney Haas, Louis A. Van Kleeck (by invitation); c] Diagnosis and traetment of coxa plana and epiphysioliathesis, Beckett Howorth; d] Serum sickness and anaphylaxis in 6211 cases treated with different kinds of horse serum, Ferdinand Kojis (by invitation). ¶ General discussion. ¶ Executive session.

MARCH 15—*Section of Orthopedic Surgery.* Executive session—a] Reading of the minutes; b] Appointment of nominating committee. ¶ Presentation of cases —a] Mobile knee after synostosis, Lewis Clark Wagner. ¶ Papers of the evening —a] Treatment of ununited fractures

of the neck of the femur—subtrochanteric osteotomy, James S. Speed, Memphis (by invitation). ¶ Discussion—Samuel Kleinberg; b] Present methods of treatment of cerebral palsy, Winthrop M. Phelps, Baltimore (by invitation). ¶ Discussion—Arthur Krida. ¶ General discussion.

March 18—*Section of Ophthalmology*—Instruction hour—Evaluation of present methods of refraction, Benjamin Friedman; Demonstration—Instruments used in the diagnosis and correction of reading disability. ¶ Executive session—a] Reading of the minutes; b] Appointment of nominating committee. ¶ Papers of the evening—a] Reading retardation: a problem to be solved cooperatively, Stella S. Center Litt.D., Director, Reading Clinic, N. Y. University (by invitation); b] Reading disability from a neurological viewpoint, Earl C. Chesher (by invitation); c] The effect of vision on reading disability, Brittain F. Payne. ¶ Discussion—Conrad Berens. ¶ General discussion.

March 19—*Combined Meeting Section of Surgery and the Section of Medicine.* Executive session—a] Reading of the minutes; b] Appointment of nominating committee for each Section. ¶ Papers of the evening—a] Mechanism and medical management of chronic ulcerative colitis, Thomas T. Mackie, Moore A. Mills (by invitation; b] Surgical treatment of chronic ulcerative colitis, Henry W. Cave. ¶ Discussion—Burrill Crohn, John H. Garlock. ¶ General discussion.

March 20—*Section of Genito-Urinary Surgery.* Executive session—a] Reading of the minutes; b] Appointment of nominating committee. ¶ Papers of the evening—Symposium on prostatectomy—a] A suggested new type of anesthesia for prostatic surgery, John A. Taylor; b] Transurethral management of prostatic disease in patients over 75 years of age (motion picture), Alf H. Gunderson, LaCrosse, Wis. (by invitation); c] Suprapubic prostatectomy; its differential indications and limitations; modifications in technique (motion picture), Clifford W. Losh, Des Moines, Ia. (by invitation); d] Perineal prostatectomy; a statistical survey; indications and technique (motion picture), J. A. Campbell Colston, Baltimore (by invitation). ¶ General discussion — Nathaniel P. Rathbun, George F. Hoch.

March 20—*Combined Meeting Sections of Otolaryngology of The New York Academy of Medicine and the Philadelphia College of Physicians.* Before the meetting there was a demonstration in the anteroom of postoperative results. ¶ Executive session—Section of Otolaryngology of the Academy—a] Reading of the minutes; b] Appointment of nominating committee. ¶ Paper of the evening—Endaural fenestration of the horizontal semicircular canal for otosclerosis. Indications, technique, observations as to early and late postoperative results, Julius Lempert (by invitation). ¶ Discussion—Edward Campbell, Philadelphia (by invitation), George Shambaugh, Jr., Chicago, (by invitation), Joseph Sullivan, Toronto, (by invitation) William Greenfield, Hackensack (by invitation).

March 26—*Section of Obstetrics and Gynecology.* Executive Session—a] Reading of the minutes; b] Appointment of nominating committee. ¶ "Asphyxia Neonatorum" (moving pictures), Henry Rascoff (by invitation). ¶ From the Gynecological Service, Harlem Hospital—a] Presentation of cases—Abdominal pregnancy with unusual complication, Elias Rauch (by invitation); b] Papers of the evening—1] Differential sign between giant ovarian cysts and ascites (lantern slides), George Blinich (by invitation); 2] A simple method of therapeutic abortion combined with sterilization (lantern slides), Avraam Shukuris (by invitation); 3] Photography of the cervix, Henry C. Falk.